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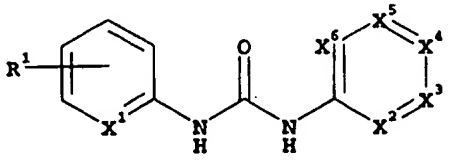
(54) Title: SUBSTITUTED β-ALANINES



(I)

(57) Abstract

The invention is directed to physiologically active compounds of general formula (I), wherein R^1 is hydrogen, halogen, lower alkyl or lower alkoxy; X^1, X^2 and X^6 independently represent N or CR^2; and one of X^3, X^4 and X^5 represents CR^3 and the others independently represents N or CR^2 [where R^2 is hydrogen, halogen, lower alkyl or lower alkoxy; and R^3 represents a group $-L^1-(CH_2)_n-C(=O)-N(R^4)-CH_2-CH_2-Y$]; and their prodrugs, and pharmaceutically acceptable salts and solvates of such compounds and their prodrugs. Such compounds have valuable pharmaceutical properties, in particular the ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4($\alpha 4\beta 1$).

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SUBSTITUTED β-ALANINES

This invention is directed to substituted β-alanines, their preparation, pharmaceutical compositions containing these compounds, and their pharmaceutical use in the treatment of disease states capable of being modulated by the inhibition of cell adhesion.

Cell adhesion is a process by which cells associate with each other, migrate towards a specific target or localise within the extra-cellular matrix. Many of the cell-cell and cell-extracellular matrix interactions are mediated by protein ligands (e.g. fibronectin, vitronectin and VCAM-1) and their integrin receptors [e.g. VLA-4 ($\alpha_4\beta_1$)]. Recent studies have shown these interactions to play an important part in many physiological (e.g. embryonic development and wound healing) and pathological conditions (e.g. tumour-cell invasion and metastasis, inflammation, atherosclerosis and autoimmune disease).

A wide variety of proteins serve as ligands for integrin receptors. In general, the proteins recognised by integrins fall into one of three classes: extracellular matrix proteins, plasma proteins and cell surface proteins. Extracellular matrix proteins such as collagen fibronectin, fibrinogen, laminin, thrombospondin and vitronectin bind to a number of integrins. Many of the adhesive proteins also circulate in plasma and bind to activated blood cells. Additional components in plasma that are ligands for integrins include fibrinogen and factor X. Cell bound complement C3bi and several transmembrane proteins, such as Ig-like cell adhesion molecule (ICAM-1,2,3) and vascular cell adhesion molecule (VCAM-1), which are members of the Ig superfamily, also serve as cell-surface ligands for some integrins.

Integrins are heterodimeric cell surface receptors consisting of two subunits called α and β. There are at least twelve different α-subunits (α1-α6, α-L, α-M, α-X, α-IIb, α-V and α-E) and at least nine different β (β1-β9) subunits. The integrin family can be subdivided into classes based on the β subunits, which can be associated with one or more α-subunits. The most widely distributed integrins belong to the β1 class, also known as the very late antigens (VLA). The second class of integrins are leukocyte specific receptors and consist of one of three α-subunits (α-L, α-M or α-X) complexed with the β2 protein. The cytoadhesins α-IIbβ3 and α-Vβ3, constitute the third class of integrins.

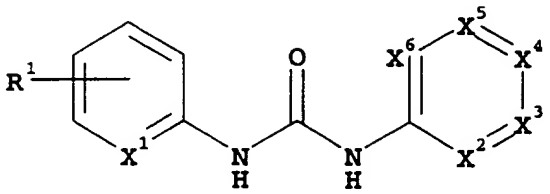
The present invention principally relates to agents which modulate the interaction of the ligand VCAM-1 with its integrin receptor α4β1 (VLA-4), which is expressed on numerous hematopoietic cells and established cell lines, including hematopoietic precursors, peripheral and cytotoxic T lymphocytes, B lymphocytes, monocytes, thymocytes and eosinophils.

The integrin α4β1 mediates both cell-cell and cell-matrix interactions. Cells expressing α4β1 bind to the carboxy-terminal cell binding domain of the extracellular matrix protein fibronectin, to the cytokine-inducible endothelial cell surface protein VCAM-1, and to each other to promote homotypic aggregation. The expression of VCAM-1 by endothelial cells is upregulated by proinflammatory cytokines such as INF-γ, TNF-α and LI-1β.

Regulation of α4β1 mediated cell adhesion is important in numerous physiological processes, including T-cell proliferation, B-cell localisation to germinal centres, and adhesion of activated T-cells and eosinophils to endothelial cells. Evidence for the involvement of VLA-4/VCAM-1 interaction in various disease processes such as melanoma cell division in metastasis, T-cell infiltration of synovial membranes in rheumatoid arthritis, autoimmune diabetes, collitis and leukocyte penetration of the blood-brain barrier in experimental autoimmune encephalomyelitis, atherosclerosis, peripheral vascular disease, cardiovascular disease and multiple sclerosis, has been accumulated by investigating the role of the peptide CS-1 (the variable region of fibronectin to which α4β1 binds via the sequence Leu-Asp-Val) and antibodies specific for VLA-4 or VCAM-1 in various in vitro and in vivo experimental models of inflammation. For example, in a Streptococcal cell wall-induced experimental model of arthritis in rats, intravenous administration of CS-1 at the initiation of arthritis suppresses both acute and chronic inflammation (S.M.Wahl et al., J.Clin.Invest., 1994, 94, pages 655-662). In the oxazalone-sensitised model of inflammation (contact hypersensitivity response) in mice, intravenous administration of anti-α4 specific monoclonal antibodies significantly inhibited (50-60% reduction in the ear swelling response) the efferent response (P.L.Chisholm et al. J.Immunol., 1993, 23, pages 682-688).

We have now found a novel group of substituted β-alanines which have valuable pharmaceutical properties, in particular the ability to regulate the interaction of VCAM-1 and fibronectin with the integrin VLA-4 (α4β1).

Thus, in one aspect, the present invention is directed to compounds of general formula (I):-



(I)

wherein:-

R^1 is hydrogen, halogen, lower alkyl or lower alkoxy;

X^1, X^2 and X^6 independently represent N or CR^2; and

one of X^3, X^4 and X^5 represents CR^3 and the others independently represents N or CR^2

[where R^2 is hydrogen, halogen, lower alkyl or lower alkoxy; and R^3 represents a group $-L^1-(CH_2)_n-C(=O)-N(R^4)-CH_2-CH_2-Y$ in which:

R^4 is aryl or heteroaryl, or R^4 is alkyl, alkenyl, alkynyl each optionally substituted by one or more groups chosen from halo, oxo, R^5, $-C(=O)-R^7$, $-NH-C(=O)-R^7$or $-C(=O)NY^1Y^2$, or R^4 is cycloalkenyl, cycloalkyl or heterocycloalkyl each optionally substituted by one or more groups chosen from oxo, R^6 or $-L^2-R^6$ {where R^5 is an acidic functional group (or corresponding protected derivative), aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocycloalkyl, $-ZR^7$ or $-NY^1Y^2$; R^6 is an acidic functional group (or corresponding protected derivative), aryl, heteroaryl, heterocycloalkyl, -ZH, $-Z^1R^7$ or $-NY^1Y^2$; R^7 is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; L^2 is alkylene; Y^1 and Y^2 are independently hydrogen, acyl, alkyl [optionally substituted by hydroxy, heterocycloalkyl, or one or more carboxy or $-C(=O)-NHR^8$ groups (where R^8 is hydrogen or lower alkyl)], alkylsulphonyl, aryl, arylalkyloxycarbonyl, arylsulphonyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; or the group $-NY^1Y^2$ may form a 5-7 membered cyclic amine which (i) may be optionally substituted with one or more substituents selected from carboxamido, carboxy, hydroxy, oxo, hydroxyalkyl, $HOCH_2CH_2-(OCH_2CH_2)_m-$ (where m is zero, or an integer one or two), or alkyl optionally substituted by carboxy or carboxamido (ii) may also contain a further heteroatom selected from O, N, S or SO_2 and (iii) may also be fused to additional aromatic, heteroaromatic.

heterocycloalkyl or cycloalkyl rings to form a bicyclic or tricyclic ring system; Z is O or S; and Z^1 is O or $S(O)_m$};

L^1 represents a $-R^9-R^{10}-$ linkage, in which R^9 is a straight or branched C_{1-6}alkylene chain, a straight or branched C_{2-6}alkenylene chain or a straight or branched C_{2-6}alkynylene chain, and R^{10} is a direct bond, cycloalkylene, heterocycloalkylene, arylene, heteroaryldiyl, $-C(=Z)-NR^{11}-$, $-NR^{11}-C(=Z)-$, $-Z^1-$, $-NR^{11}-$, $-C(=O)-$, $-C(=NOR^{11})-$, $-NR^{11}-C(=Z)-NR^{11}-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-O-C(=O)-$, $-C(=O)-O-$, $-NR^{11}-C(=O)-O-$ or $-O-C(=O)-NR^{11}-$ (where R^{11} is a hydrogen atom or R^4); but excluding compounds where an oxygen, nitrogen or sulphur atom is attached directly to a carbon carbon multiple bond;

Y is carboxy (or an acid bioisostere) or $-C(=O)-NY^1Y^2$; and

n is an integer from 1 to 6];

and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

In the present specification, the term "compounds of the invention", and equivalent expressions, are meant to embrace compounds of general formula (I) as hereinbefore described, which expression includes the prodrugs, the pharmaceutically acceptable salts, and the solvates, e.g. hydrates, where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text, but these instances are purely illustrative and it is not intended to exclude other instances when the context so permits.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:-

"Patient" includes both human and other mammals.

"Acid bioisostere" means a group which has chemical and physical similarities producing broadly similar biological properties to a carboxy group (see Lipinski, Annual Reports in Medicinal Chemistry, 1986,21,p283 "Bioisosterism In Drug Design"; Yun, Hwahak Sekye, 1993,33,p576-579 "Application Of Bioisosterism To New Drug Design"; Zhao, Huaxue Tongbao,

1995,p34-38 "Bioisosteric Replacement And Development Of Lead Compounds In Drug Design"; Graham, Theochem, 1995,343,p105-109 "Theoretical Studies Applied To Drug Design:ab initio Electronic Distributions In Bioisosteres"). Examples of suitable acid bioisosteres include: -C(=O)-NHOH, -C(=O)-CH_2OH, -C(=O)-CH_2SH, -C(=O)-NH-CN, sulpho, phosphono, alkylsulphonylcarbamoyl, tetrazolyl, arylsulphonylcarbamoyl, heteroarylsulphonylcarbamoyl, N-methoxycarbamoyl, 3-hydroxy-3-cyclobutene-1,2-dione, 3,5-dioxo-1,2,4-oxadiazolidinyl or heterocyclic phenols such as 3-hydroxyisoxazolyl and 3-hydoxy-1-methylpyrazolyl.

"Acidic functional group" means a group with an acidic hydrogen within it. The "corresponding protected derivatives" are those where the acidic hydrogen atom has been replaced with a suitable protecting group. For suitable protecting groups see T.W. Greene and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. Exemplary acidic functional groups include carboxyl (and acid bioisosteres), hydroxy, mercapto and imidazole. Exemplary protected derivatives include esters of carboxy groups, ethers of hydroxy groups, thioethers of mercapto groups and N-arylalkyl(e.g. N-benzyl) derivatives of imidazoles.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as described herein.

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. "Branched", as used herein and throughout the text, means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear chain; here a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, cyclohexylbutenyl and decenyl.

"Alkenylene" means an aliphatic bivalent radical derived from a straight or branched alkenyl group, in which the alkenyl group is as described herein. Exemplary alkenylene radicals include C_{2-4}alkenylene radicals such as vinylene and propylene.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as described herein. Exemplary alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy and heptoxy.

"Alkoxycarbonyl" means an alkyl-O-CO- group in which the alkyl group is as described herein. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Alkyl" means, unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 15 carbon atoms in the chain optionally substituted by one or more halogen atoms. Particular alkyl groups have from 1 to about 6 carbon atoms. "Lower alkyl" as a group or part of a lower alkoxy group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 4 carbon atoms in the chain. Exemplary alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl.

"Alkylene" means an aliphatic bivalent radical derived from a straight or branched alkyl group, in which the alkyl group is as described herein. Exemplary alkylene radicals include C_{1-4}alkylene radicals such as methylene, ethylene and trimethylene.

"Alkylsulphinyl" means an alkyl-SO- group in which the alkyl group is as previously described. Preferred alkylsulphinyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylsulphonyl" means an alkyl-SO_2- group in which the alkyl group is as previously described. Preferred alkylsulphonyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylsulphonylcarbamoyl" means an alkyl-SO_2-NH-C(=O)- group in which the alkyl group is as previously described. Preferred alkylsulphonylcarbamoyl groups are those in which the alkyl group is C_{1-4}alkyl.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, isopropylthio and heptylthio.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain.

Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butynyl, i-butynyl, 3-methylbut-2-ynyl, and n-pentynyl.

"Alkynylene" means an aliphatic bivalent radical derived from a straight or branched alkynyl group, in which the alkynyl group is as described herein. Exemplary alkynylene radicals include C_{2-4}alkynylene radicals such as ethynylene and propynylene.

"Aroyl" means an aryl-CO- group in which the aryl group is as described herein. Exemplary aroyl groups include benzoyl and 1- and 2-naphthoyl.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as previously defined.

"Aryl" as a group or part of a group denotes: (i) an optionally substituted monocyclic or multicyclic aromatic carbocyclic moiety of about 6 to about 14 carbon atoms or (ii) an optionally substituted partially saturated multicyclic aromatic carbocyclic moiety in which an aryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure such as a tetrahydronaphthyl, indenyl or indanyl ring. When R^4 contains an optionally substituted aryl group, this may particularly represent optionally substituted phenyl with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes, for example, acyl, acylamino, alkoxy, alkoxycarbonyl, alkylsulphinyl, alkylsulphonyl, alkylthio, aroyl, aroylamino, aryl, arylalkyloxy, arylalkyloxycarbonyl, arylalkylthio, aryloxy, aryloxycarbonyl, arylsulphinyl, arylsulphonyl, arylthio, carboxy, cyano, halo, heteroaroyl, heteroaryl, heteroarylalkyloxy, heteroarylamino, heteroaryloxy, hydroxy, nitro, trifluoromethyl, Y^3Y^4N-, Y^3Y^4NCO-, $Y^3Y^4NSO_2$-(where Y^3 and Y^4 are independently hydrogen, alkyl, aryl, and arylalkyl), Y^3Y^4N-L^3-Z^2- (where L^3 is C_{2-6}alkylene and Z^2 is O, NR^8 or $S(O)_m$), alkylC(=O)-Y^3N-, alkylSO_2-Y^3N- or alkyl optionally substituted with aryl, heteroaryl, hydroxy, or Y^3Y^4N-.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C_{1-4}alkyl moiety. Exemplary arylalkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Arylalkyloxy" means an arylalkyl-O- group in which the arylalkyl groups is as previously described. Exemplary arylalkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Arylalkyloxycarbonyl" means an arylalkyl-O-CO- group in which the arylalkyl groups is as previously described. An exemplary arylalkyloxycarbonyl group is benzyloxycarbonyl.

"Arylalkylthio" means an arylalkyl-S- group in which the arylalkyl group is as previously described. An exemplary arylalkylthio group is benzylthio.

"Arylene" means an optionally substituted bivalent radical derived from an aryl group as defined above. Exemplary arylene groups include optionally substituted phenylene, naphthylene and indanylene. Suitable substituents include one or more "aryl group substituents" as defined above, particularly halogen, methyl or methoxy.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include optionally substituted phenoxy and naphthoxy.

"Aryloxycarbonyl" means an aryl-O-CO- group in which the aryl group is as previously described. Exemplary aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl.

"Arylsulphinyl" means an aryl-SO- group in which the aryl group is as previously described.

"Arylsulphonyl" means an aryl-SO_2- group in which the aryl group is as previously described.

"Arylsulphonylcarbamoyl" means an aryl-SO_2-NH-C(=O)- group in which the aryl group is as previously described.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Azaheteroaryl" means an aromatic carbocyclic moiety of about 5 to about 10 ring members in which one of the ring members is nitrogen and the other ring members are chosen from carbon,

oxygen, sulphur, or nitrogen. Examples of azaheteroaryl groups include pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinazolinyl, imidazolyl, and benzimidazolyl.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing at least one carbon-carbon double bond and having about 3 to about 10 carbon atoms. Exemplary monocyclic cycloalkenyl rings include C_{3-8}cycloalkenyl rings such as cyclopentenyl, cyclohexenyl or cycloheptenyl.

"Cycloalkyl" means a saturated monocyclic or bicyclic ring system of about 3 to about 10 carbon atoms optionally substituted by oxo. Exemplary monocyclic cycloalkyl rings include C_{3-8}cycloalkyl such as cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocyclic cycloalkylalkyl groups include C_{3-8}cycloalkylC_{1-4}alkyl groups such as cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

"Cycloalkylene" means a divalent radical derived from a cycloalkyl group as defined above. Exemplary cycloalkylene radicals include C_{3-8}cycloalkylene radicals such as cyclopentylene and cyclohexylene.

"Halo" or "halogen" means fluoro, chloro, bromo, or iodo. Preferred are fluoro or chloro.

"Heteroaroyl" means a heteroaryl-CO- group in which the heteroaryl group is as described herein. Exemplary groups include pyridylcarbonyl.

"Heteroaryl" as a group or part of a group denotes: (i) an optionally substituted aromatic monocyclic or multicyclic organic moiety of about 5 to about 10 ring members in which one or more of the ring members is/are element(s) other than carbon, for example nitrogen, oxygen or sulphur (examples of such groups include benzimidazolyl, benzthiazolyl, furyl, imidazolyl, indolyl, indolizinyl, isoxazolyl, isoquinolinyl, isothiazolyl, oxadiazolyl, pyrazinyl, pyridazinyl, pyrazolyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, 1,3,4-thiadiazolyl, thiazolyl, thienyl and triazolyl groups, optionally substituted by one or more aryl group substituents as defined above); (ii) an optionally substituted partially saturated multicyclic heterocarbocyclic

moiety in which a heteroaryl and a cycloalkyl or cycloalkenyl group are fused together to form a cyclic structure (examples of such groups include pyrindanyl groups). Optional substituents include one or more "aryl group substituents" as defined above. When L^1 or R^4 contains an optionally substituted heteroaryl group this may particularly represent an optionally substituted "azaheteroaryl" group.

"Heteroarylalkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a C_{1-4}alkyl moiety such as optionally substituted pyridylC_{1-4}alkyl (e.g. optionally substituted pyridylmethyl).

"Heteroarylalkyloxy" means an heteroarylalkyl-O- group in which the heteroarylalkyl group is as previously described. Preferred heteroarylalkyloxy groups include heteroarylC_{1-4}alkyloxy such as optionally substituted pyridylC_{1-4}alkyloxy (e.g. optionally substituted pyridylmethoxy).

"Heteroarylamino" means a heteroaryl-NH- group in which the heteroaryl moiety are as previously described.

"Heteroaryldiyl" means a bivalent radical derived from a heteroaryl group as defined above.

"Heteroaryloxy" means an heteroaryl-O- group in which the heteroaryl group is as previously described. Exemplary heteroaryloxy groups include optionally substituted pyridyloxy.

"Heteroarylsulphonylcarbamoyl" means a heteroaryl-SO_2-NH-C(=O)- group in which the heteroaryl group is as previously described.

"Heterocycloalkyl" means: (i) a cycloalkyl group of about 3 to 7 ring members in which one or more of the ring carbon atoms is replaced by O, S or NY^5 (where Y^5 is hydrogen, alkyl, arylalkyl, and aryl); (ii) a partially saturated bicyclic system in which an aryl or heteroaryl ring is fused to a heterocycloalkyl ring as defined in (i) above. Examples of (ii) include 1,4-benzodioxanyl, 1,3-benzodioxolyl, chromanyl, dihydrobenzofuranyl, indolinyl and dihydropyrrolopyridinyl groups).

"Heterocycloalkylalkyl" means a heterocycloalkyl-alkyl- group in which the heterocycloalkyl and alkyl moieties are as previously described.

"Heterocycloalkylene" means a bivalent radical derived from a heterocycloalkyl group as defined above.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyl groups contain C_{1-4}alkyl for example hydroxymethyl and 2-hydroxyethyl.

"Y^3Y^4N-" means a substituted or unsubstituted amino group, wherein Y^3 and Y^4 are as previously described. Exemplary groups include amino (H_2N-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

"Y^3Y^4NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y^3 and Y^4 are as previously described. Exemplary groups are carbamoyl (H_2NCO-) and dimethylcarbamoyl (Me_2NCO-).

"$Y^3Y^4NSO_2$-" means a substituted or unsubstituted sulphamoyl group, wherein Y^3 and Y^4 are as previously described. Exemplary groups are sulphamoyl (H_2NSO_2-) and dimethylsulphamoyl (Me_2NSO_2-).

"Prodrug" means a compound which is convertible in vivo by metabolic means (e.g. by hydrolysis) to a compound of formula (I), including N-oxides thereof. For example an ester of a compound of formula (I) containing a hydroxy group may be convertible by hydrolysis in vivo to the parent molecule. Alternatively an ester of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule.

Suitable esters of compounds of formula (I) containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates.

An especially useful class of esters of compounds of formula (I) containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et. al., J. Med. Chem., 1989, 32 , page 2503-2507, and include substituted (aminomethyl)-benzoates, for example dialkylamino-methylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)benzoates.

Where the compound of the invention contains a carboxy group, or a sufficiently acidic bioisostere, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including those derived from alkali and alkaline earth metal salts, within the scope of the invention include those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminium hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, tetramethylammonium hydroxide, and the like.

Some of the compounds of the present invention are basic, and such compounds are useful in the form of the free base or in the form of a pharmaceutically acceptable acid addition salt thereof.

Acid addition salts are a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate

product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention include those derived from mineral acids and organic acids, and include hydrohalides, e.g. hydrochlorides and hydrobromides, sulphates, phosphates, nitrates, sulphamates, acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-p-toluoyltartrates, methane-sulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

With reference to formula (I) above, the following are particular and preferred groupings:

R^1 may particularly represent hydrogen, especially when X^1 represents C-R^2 where R^2 is lower alkyl or lower alkoxy.

X^1 may particularly represent CR^2, especially where R^2 is C_{1-4}alkyl (e.g. methyl) or C_{1-4}alkoxy (e.g. methoxy).

X^2 may particularly represent CR^2, especially where R^2 is C_{1-4}alkyl (e.g. methyl) or C_{1-4}alkoxy (e.g. methoxy).

X^3 may particularly represent CR^2 and is preferably CH.

X^6 may particularly represent CR^2 and is preferably CH.

One of X^4 and X^5 may particularly represent CR^3 and the other represents CR^2, especially CH.

Within R^3 the moiety L^1 may particularly represent a $-R^9-R^{10}-$ linkage where R^9 represents a straight or branched C_{1-6}alkylene chain, especially a straight C_{1-4}alkylene chain such as methylene or ethylene, and R^{10} represents $-C(=Z)-NR^{11}-$, preferably $-C(=O)-NR^{11}-$ especially where R^{11} is:-

(i) hydrogen;

(ii) C_{1-6}alkyl (e.g. C_{1-4}alkyl groups such as ethyl, propyl or especially methyl);

(iii) C_{1-6}alkyl (especially C_{1-3}alkyl) substituted by R^5, where R^5 is aryl (e.g. phenyl);

(iv) C_{1-6}alkyl (especially C_{1-3}alkyl) substituted by R^5, where R^5 is heteroaryl (exemplary heteroaryl groups include indolyl, imidazolyl , pyridyl and furyl);

(v) C_{1-6}alkyl (especially C_{1-3}alkyl) substituted by R^5, where R^5 is cycloalkyl (e.g. C_{3-8}cycloalkyl such as cyclopentyl and cyclohexyl);

(vi) C_{1-6}alkyl (especially C_{1-3}alkyl) substituted by R^5, where R^5 is carboxy (or an acid bioisostere); or

(vii) C_{1-6}alkyl (e.g. C_{1-4}alkyl such as ethyl or propyl) substituted by R^5, where R^5 is $-NY^1Y^2$ (exemplary $-NY^1Y^2$ groups include acylamino, aryl(alkyl)amino, N-pyrrolidinyl and 2-oxo-N-pyrrolidinyl).

Within R^3 the moiety R^4 may particularly represent straight or branched C_{1-10}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, 1,5-dimethylhexyl, n-nonyl or n-decyl).

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is aryl. Exemplary aryl groups include phenyl optionally substituted by one or more "aryl group substituents", for example alkoxyphenyl, dialkoxyphenyl, arylalkyloxy(alkoxy)phenyl, halophenyl, dialkylaminophenyl, trifluoromethylphenyl and methanesulphonylphenyl. R^4 is preferably straight or branched C_{1-3}alkyl substituted by diC_{1-3}alkoxyphenyl and is particularly 3,4-diC_{1-3}alkoxybenzyl.

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is heteroaryl. Exemplary heteroaryl groups include indolyl, imidazolyl, pyridyl and furyl. R^4 is preferably straight or branched C_{1-3}alkyl substituted by azaheteroaryl and is particularly 3-(imidazol-1-yl)-C_{1-3}alkyl).

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is C_{3-8}cycloalkyl. R^4 is preferably straight or branched C_{1-3}alkyl substituted by C_{5-6}cycloalkyl.

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is C_{1-6}alkoxy, especially C_{1-4}alkoxy such as methoxy.

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is halo.

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is an acidic functional group. R^4 is preferably straight or branched C_{1-3}alkyl substituted by carboxy.

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is heterocycloalkyl. Exemplary heterocycloalkyl groups include benzodioxolyl and benzodioxanyl. R^4 is preferably straight or branched C_{1-3}alkyl substituted by benzodioxolyl and benzodioxanyl.

Within R^3 the moiety R^4 may also particularly represent straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by $-NY^1Y^2$. Exemplary $-NY^1Y^2$ groups include acylamino, aryl(alkylamino) and $-NY^1Y^2$ groups derived from 5-7 membered cyclic

amines such as morpholine, piperidine, pyrrolidine and 2-oxo-pyrrolidine. R^4 is preferably straight or branched C_{2-3}alkyl substituted by an N-linked 5-7 membered cyclic amine, especially 3-(2-oxo-pyrrolidin-1-yl)-C_{2-3}alkyl.

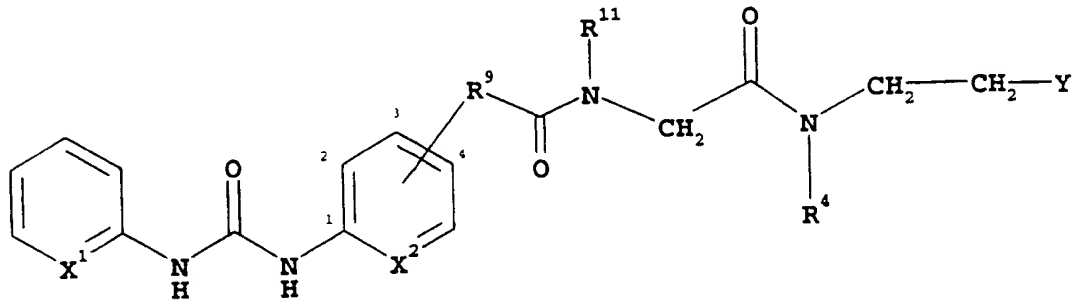
Within R^3 the moiety R^4 may also particularly represent C_{1-4}alkenyl (e.g. allyl).

Within R^3 the moiety n may particularly represent the integer 1 to 3, especially 1.

Within R^3 the moiety Y may particularly represent carboxy or an acid bioisostere, especially carboxy.

It is to be understood that this invention covers all appropriate combinations of the particular and preferred groupings referred to herein.

A particular group of compounds of the invention are compounds of formula (Ia):-



(Ia)

in which R^4, R^9, R^{11} and Y are as hereinbefore defined, X^1 and X^2 each independently represent CR^2 (wherein each R^2 group is as hereinbefore defined), and $-R^9-CON(R^{11})-CH_2-CON(R^4)-CH_2-CH_2-Y$ is attached at the ring 3 or 4 position, and their prodrugs and pharmaceutically acceptable salts, and solvates (e.g. hydrates) of compounds of formula (Ia) and their prodrugs.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-10}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, 1,5-dimethylhexyl, n-nonyl, or n-decyl) are preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is aryl are also preferred. Exemplary aryl groups include phenyl optionally substituted by one or more "aryl group substituents", for example alkoxyphenyl, dialkoxyphenyl, arylalkyloxy(akoxy)phenyl, halophenyl, dialkylaminophenyl, trifluoromethyl and methanesulphonylphenyl. Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-3}alkyl substituted by diC_{1-3}alkoxyphenyl , particularly 3,4-diC_{1-3}alkoxybenzyl (e.g. 3,4-dimethoxybenzyl 3,4-diethoxybenzyl and 3-ethoxy-4-methoxybenzyl), are especially preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is heteroaryl are also preferred. Exemplary heteroaryl groups include indolyl, imidazolyl, pyridyl and furyl. Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-3}alkyl substituted by azaheteroaryl, particularly 3-(imidazol-1-yl)-C_{1-3}alkyl (e.g. 3-(imidazol-1-yl)-propyl), are especially preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is C_{3-8}cycloalkyl are also preferred. Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-3}alkyl substituted by C_{5-6}cycloalkyl groups are especially preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is C_{1-6}alkoxy, especially C_{1-4}alkoxy (e.g. methoxy), are also preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is halo are also preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is an acidic functional group are also preferred. Compounds of formula (Ia) in which R^4 is straight or branched C_{1-3}alkyl substituted by carboxy are especially preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by R^5, where R^5 is heterocycloalkyl are also preferred. Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-3}alkyl substituted by benzodioxolyl and benzodioxanyl are especially preferred.

Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-6}alkyl (e.g. methyl, ethyl, n-propyl, i-propyl or n-butyl) substituted by $-NY^1Y^2$ are also preferred. Exemplary $-NY^1Y^2$ groups include acylamino, aryl(alkylamino) and $-NY^1Y^2$ groups derived from 5-7 membered cyclic amines such as morpholine, piperidine, pyrrolidine and 2-oxo-pyrrolidine. Compounds of formula (Ia) in which R^4 represents straight or branched C_{1-3}alkyl substituted by an N-linked 5-7 membered cyclic amine, especially 3-(2-oxo-pyrrolidin-1-yl)-C_{1-3}alkyl (e.g. 3-(2-oxo-pyrrolidin-1-yl)-propyl), are particularly preferred.

Compounds of formula (Ia) in which R^4 represents C_{1-4}alkenyl (e.g. allyl) are also preferred.

Compounds of formula (Ia) in which R^9 represents a straight or branched C_{1-6}alkylene chain, especially a straight or branched C_{1-4}alkylene chain, more especially methylene, are preferred.

Compounds of formula (Ia) in which R^{11} represents hydrogen are preferred.

Compounds of formula (Ia) in which R^{11} represents straight or branched C_{1-4}alkyl, particularly methyl, are also preferred.

Compounds of formula (Ia) in which R^{11} represents straight or branched C_{1-3}alkyl substituted by R^5, where R^5 is aryl (e.g. phenyl), are also preferred. Compounds of formula (Ia) in which R^{11} represents straight chain C_{1-3}alkyl substituted by phenyl are especially preferred.

Compounds of formula (Ia) in which R^{11} represents straight or branched C_{1-3}alkyl substituted by R^5, where R^5 is heteroaryl, are also preferred. Exemplary heteroaryl groups include indolyl, imidazolyl, pyridyl and furyl. Compounds of formula (Ia) in which R^{11} represents straight chain C_{1-3}alkyl substituted by azaheteroaryl (e.g. imidazolyl or pyridyl) are especially preferred.

Compounds of formula (Ia) in which R^{11} represents straight or branched C_{1-3}alkyl substituted by R^5, where R^5 is cycloalkyl (e.g. C_{3-8}cycloalkyl), are also preferred. Exemplary C_{3-8}cycloalkyl groups include cyclopentyl and cyclohexyl. Compounds of formula (Ia) in which R^{11} represents straight chain C_{1-3}alkyl substituted by cyclohexyl are especially preferred.

Compounds of formula (Ia) in which R^{11} represents straight or branched C_{1-3}alkyl substituted by carboxy are also preferred.

Compounds of formula (Ia) in which R^{11} represents straight or branched C_{2-3}alkyl (e.g. ethyl and n-propyl) substituted by $-NY^1Y^2$ are also preferred. Exemplary $-NY^1Y^2$ groups include acylamino, aryl(alkyl)amino and $-NY^1Y^2$ groups derived from 5-7 membered cyclic amines such as pyrrolidine and 2-oxo-pyrrolidine. Compounds of formula (Ia) in which R^{11} represents ethyl or propyl substituted by 3-(2-oxo-pyrrolidin-1-yl), especially 3-(2-oxo-pyrrolidin-1-yl)-propyl, are preferred.

Compounds of formula (Ia) in which X^1 represents CR^2 where R^2 is C_{1-4}alkyl or C_{1-4}alkoxy (e.g. methyl or methoxy), especially methyl, are preferred.

Compounds of formula (Ia) in which X^2 represents CR^2 where R^2 is hydrogen or C_{1-4}alkoxy, especially methoxy, are also preferred.

Compounds of formula (Ia) in which Y represents carboxy are preferred.

The group -R^9-C(=O)-N(R^{11})-CH_2-C(=O)-NR^4-CH_2-CH_2-Y may preferably be attached at the ring 4 position.

A preferred group of compounds of the invention are compounds of formula (Ia) in which:- R^4 is C_{1-10}alkyl, C_{1-6}alkyl substituted by aryl (especially 3,4-dimethoxyphenylC_{1-3}alkyl), C_{1-6}alkyl substituted by heteroaryl (especially 3-(imidazol-1-yl)-propyl), C_{1-6}alkyl substituted by cycloalkyl (especially cyclopentyl- and cyclohexyl-C_{1-3}alkyl), C_{1-6}alkyl substituted by heterocycloalkyl (especially C_{1-3}alkyl substituted by benzodioxolyl and benzodioxanyl), C_{1-6}alkyl substituted by C_{1-6}alkoxy, C_{1-6}alkyl substituted by halo, C_{1-6}alkyl substituted by -NY^1Y^2, [especially (2-oxo-pyrrolidin-1-yl)propyl], or C_{1-4}alkenyl (e.g. allyl); R^{11} represents hydrogen, C_{1-4}alkyl (especially methyl), C_{1-3}alkyl substituted by aryl (especially phenylC_{1-3}alkyl), C_{1-3}alkyl substituted by heteroaryl (especially imidazol-1-ylC_{1-3}alkyl and pyridylC_{1-3}alkyl), C_{1-3}alkyl substituted by C_{3-8}cycloalkyl (especially cyclohexylC_{1-3}alkyl), C_{1-3}alkyl substituted by carboxy (especially -$(CH_2)_3CO_2H$), or C_{2-3}alkyl substituted by -NY^1Y^2 [especially (2-oxo-pyrrolidin-1-yl)propyl]; R^9 represents a straight or branched C_{1-4}alkylene chain, (preferably methylene); X^1 represents CR^2 where R^2 is C_{1-4}alkyl (especially methyl); X^2 represent CR^2 where R^2 is C_{1-4}alkoxy (e.g. methoxy); Y represents carboxy; and the group -R^9-C(=O)-N(R^{11})-CH_2-C(=O)-NR^4-CH_2-CH_2-Y is attached at the ring 4 position; and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

Particular compounds of the invention are selected from the following:
3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound A;
3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(3-imidazol-1-yl)-prop-1-yl]-amino}-propionic acid, Compound B;
3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound C;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound D;

3-[[2-(ethyl-m-tolyl-amino)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound E;

3-[(2-acetylamino-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound F;

3-[(2-chloro-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound G;

3-[(3-methoxy-prop-1-yl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound H;

3-[cyclohexylmethyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound I;

3-[(4-methoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound J;

3-[isobutyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound K;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(1-phenyl-ethyl)-amino]-propionic acid, Compound L;

3-{({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-[4-(5H-1,2,4-[1,2,3]thiadiazol-4-yl)-benzyl]-amino}-propionic acid, Compound M;

3-[[1-(4-fluoro-phenyl)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound N;

3-[(2-ethoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound O;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(2-pyridin-2-yl-ethyl)-amino]-propionic acid, Compound P;

3-[[2-(3-bromo-4-methoxy-phenyl)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound Q;

3-[(3-methoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound R;

3-[(2-methoxy-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound S;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(3-methyl-butyl)-amino]-propionic acid, Compound T;

3-({[2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-[2-(4-phenoxy-phenyl)-ethyl]-amino}-propionic acid, Compound U;

3-[(2-benzo[1,3]dioxol-5-yl-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl] -acetylamino}-acetyl)-amino]-propionic acid, Compound V;

3-[butyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound W;

3-[[2-(3,5-dimethoxy-phenyl)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound X;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(furan-2-y-methyl)-amino]-propionic acid, Compound Y;

3-[allyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound Z;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-pyridin-3-ylmethyl-amino]-propionic acid, Compound AA;

3-[(3-chloro-prop-1-yl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AB;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(3-phenyl-prop-1-yl)-amino]-propionic acid, Compound AC;

3-[(2-methoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AD;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(2-morpholin-4-yl-ethyl)-amino]-propionic acid, Compound AE;

3-[(4-methanesulfonyl-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AF;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-methyl-amino]-propionic acid, Compound AG;

3-{({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-[2-(naphthalen-2-ylamino)-ethyl]-amino}-propionic acid, Compound AH;

3-[[2-(2,3-dimethoxy-phenyl)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AI;

3-[(2-diethylamino-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AJ;

3-[(1,5-dimethyl-hexyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AK;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-pentyl-amino]-propionic acid, Compound AL;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-octyl-amino]-propionic acid, Compound AM;

3-[[2-(2h-indol-3-yl)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AN;

3-[(2,3-dimethoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AO;

3-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-prop-1-yl-amino]-propionic acid, Compound AP;

3-[(3,3-diphenyl-prop-1-yl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AQ;

3-[(2,2-diphenyl-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AR;

3-[[2-(5-methoxy-2h-indol-3-yl)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AS;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(4-phenyl-butyl)-amino]-propionic acid, Compound AT;

3-[hexyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AU;

3-[benzo[1,3]dioxol-5-ylmethyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AV;

3-[(2-acetylamino-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AW;

3-{({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-[2-(4-nitro-phenyl)-ethyl]-amino}-propionic acid, Compound AX;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(2-oxo-azepan-3-yl)-amino]-propionic acid, Compound AY;

3-[(3,5-dimethoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AZ;

3-[(3-dimethylamino-prop-1-yl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BA;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-naphthalen-1-ylmethyl-amino]-propionic acid, Compound BB;

3-[(1-cyclohexyl-ethyl)-({2-[3-methoxy-4-(3-[illegible]ylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BC;

3-[N-(3,4-dimethoxybenzyl)-2-{2-[3-methoxy-4-(3-o-tolylureido)phenyl]acetylamino}acetamido]-propionic acid, alternative name: 3-[(3,4-dimethoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BD;

3-[(2-diethylamino-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BE;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(4-nitro-benzyl)-amino]-propionic acid, Compound BF;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(2-piperidin-1-yl-ethyl)-amino]-propionic acid, Compound BG;

3-[benzyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BH;

3-[cyclohexyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BI;

3-[isobutyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BJ;

3{(3-imidazol-1-yl-prop-1-yl)--[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound BK;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(4-trifluoromethyl-benzyl)-amino]-propionic acid, Compound BL;

3-[(2-methoxy-ethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BM;

3-{({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-[2-(7-methyl-2h-indol-3-yl)-ethyl]-amino}-propionic acid, Compound BN;

3-[(4-dimethylamino-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BO;

3-[isopropyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BP;

3-[(6-chloro-2-phenoxy-phenylmethyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BQ;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-phenethyl-amino]-propionic acid, Compound BR;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(1-methyl-2-phenoxy-ethyl)-amino]-propionic acid, Compound BS;

3-[[2-(5-methoxy-2H-indol-3-yl)-ethyl]-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BT;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(3-phenyl-prop-1-yl)-amino]-propionic acid, Compound BU;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-prop-1-ylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound BV;

Compounds BW to KV;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid; Compound KW;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amino}-propionic acid; Compound KX;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid; Compound LA;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amino}-propionic acid; Compound LB;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(2-carboxy-ethyl)-amino}-propionic acid; Compound LC;

3-{(2,3-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound AO;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-phenyl-amino}-propionic acid; Compound LD;

3-{(3-ethoxy-4-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LE;

3-{(3,4-diethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LF;

3-{(4-benzyloxy-3-methoxy -benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LG;

3-{[(1,4-benzodioxan-6-yl)-methyl]-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LH;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-methanesulphonylamino-prop-1-yl)-amino}-propionic acid; Compound LI;

3-[(4-dimethylamino-benzyl)-[{2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-N-methylamino]-propionic acid;

3-{(3-nitro-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LJ;

3-{(2-thienylmethyl)-({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino}-acetyl)-amino}-propionic acid, Compound LK;

3-{(2-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid; Compound LL;

3-{(4-methyl-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LM;

3-{(3,4-methylenedioxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LN;

3-{(3,5-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LO;

3-{(2-pyridylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LP;

3-{(2-furanylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LQ;

3-{(2-ethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LR;

3-{(2-thienylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LS;

3-{(4-pyridylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LT;

3-{(2-pyridylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LU;

3-{(3-nitro-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LV;

3-{(3-pyridylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LW;

3-{(4-[1,2,3-thiadiazol-4-yl]-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LX;

3-{(4-pyridylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LY;

3-{(benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LZ;

3-{(2-bromo-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound MA;

3-{(2-bromo-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound MB;

3-{(2-chloro-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound MC;

3-{(4-methanesulphonyl-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound MD;

and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

Preferred compounds of the invention include:

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound A;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(3-imidazol-1-yl)-prop-1-yl]-amino}-propionic acid, Compound B;

3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound C;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound D;

3-[allyl-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound Z;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(3-phenyl-prop-1-yl)-amino]-propionic acid, Compound AC;

3-[(2,3-dimethoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AO;

3-[({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-(4-phenyl-butyl)-amino]-propionic acid, Compound AT;

3-[N-(3,4-dimethoxybenzyl)-2-{2-[3-methoxy-4-(3-o-tolylureido)phenyl]acetylamino}acetamido]-propionic acid, Compound BD;

3{(3-imidazol-1-yl-prop-1-yl)--[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound BK;

3-[(4-dimethylamino-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound BO;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid; Compound KW;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amino}-propionic acid; Compound KX;

3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound KY;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid; Compound LA;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(2-carboxy-ethyl)-amino}-propionic acid; Compound LC;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-phenyl-amino}-propionic acid; Compound LD;

3-{(3-ethoxy-4-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LE;

3-{(3,4-diethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LF;

3-{(4-benzyloxy-3-methoxy -benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LG;

3-{[(1,4-benzodioxan-6-yl)-methyl]-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LH;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-methanesulphonylamino-prop-1-yl)-amino}-propionic acid; Compound LI;

3-{(3-nitro-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LJ;

3-{(2-thienylmethyl)-({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino}-acetyl)-amino}-propionic acid, Compound LK;

3-{(2-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid; Compound LL;

3-{(4-methyl-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LM;

3-{(3,4-methylenedioxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LN;

3-{(3,5-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LO;

3-{(2-pyridylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LP;

3-{(2-furanylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LQ;

3-{(2-ethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound LR;

3-{(2-thienylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LS;

3-{(4-pyridylmethyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid, Compound LT;

and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

Especially preferred compounds of the invention include:

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound A;

3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound C;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound D;

3-[(2,3-dimethoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AO;

3-[N-(3,4-dimethoxybenzyl)-2-{2-[3-methoxy-4-(3-o-tolylureido)phenyl]acetylamino}acetamido]-propionic acid, Compound BD;

3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid; Compound KW;

3-{(3-ethoxy-4-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LE;

3-{(3,4-diethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LF;

and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

The compounds of the invention exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. The present invention thus provides, according to a further

ıspect, compounds of the invention and compositions containing compounds of the invention for use in therapy.

Compounds within the scope of the present invention block the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha4\beta1$) according to tests described in the literature and described in vitro and in vivo procedures hereinafter, and which tests results are believed to correlate to pharmacological activity in humans and other mammals. Thus, in a further embodiment, the present invention provides compounds of the invention and compositions containing compounds of the invention for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha4\beta1$ mediated cell adhesion. For example, compounds of the present invention are useful in the treatment of inflammatory diseases, for example joint inflammation, including arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis and osteoarthritis. Additionally, the compounds are useful in the treatment of acute synovitis, autoimmune diabetes, autoimmune encephalomyelitis, collitis, atherosclerosis, peripheral vascular disease, cardiovascular disease, multiple sclerosis, asthma, psoriasis restenosis, myocarditis, inflammatory bowel disease and melanoma cell division in metastasis.

A special embodiment of the therapeutic methods of the present invention is the treating of asthma.

Another special embodiment of the therapeutic methods of the present invention is the treating of joint inflammation.

Another special embodiment of the therapeutic methods of the present invention is the treating of inflammatory bowel disease.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha4\beta1$), for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of the invention or a composition containing a compound of the invention. "Effective amount" is meant to describe

an amount of compound of the present invention effective in inhibiting the interaction of the ligand VCAM-1 to its integrin receptor VLA-4 ($\alpha 4\beta 1$), and thus producing the desired therapeutic effect.

References herein to treatment should be understood to include prophylactic therapy as well as treatment of established conditions.

The present invention also includes within its scope pharmaceutical compositions comprising at least one of the compounds of the invention in association with a pharmaceutically acceptable carrier or excipient.

Compounds of the invention may be administered by any suitable means. In practice compounds of the present invention may generally be administered parenterally, topically, rectally, orally or by inhalation, especially by the oral route.

Compositions according to the invention may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavourings, colourings, or stabilisers in order to obtain pharmaceutically acceptable preparations. The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the active compound, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or

aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilised by heating, irradiation or microfiltration.

For topical administration, gels (water or alcohol based), creams or ointments containing compounds of the invention may be used. Compounds of the invention may also be incorporated in a gel or matrix base for application in a patch, which would allow a controlled release of compound through the transdermal barrier.

For administration by inhalation compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebuliser or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of the invention.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.001 to about 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The compounds according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. Of course, for some patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C.Larock in Comprehensive Organic Transformations, VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P.G.M.Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

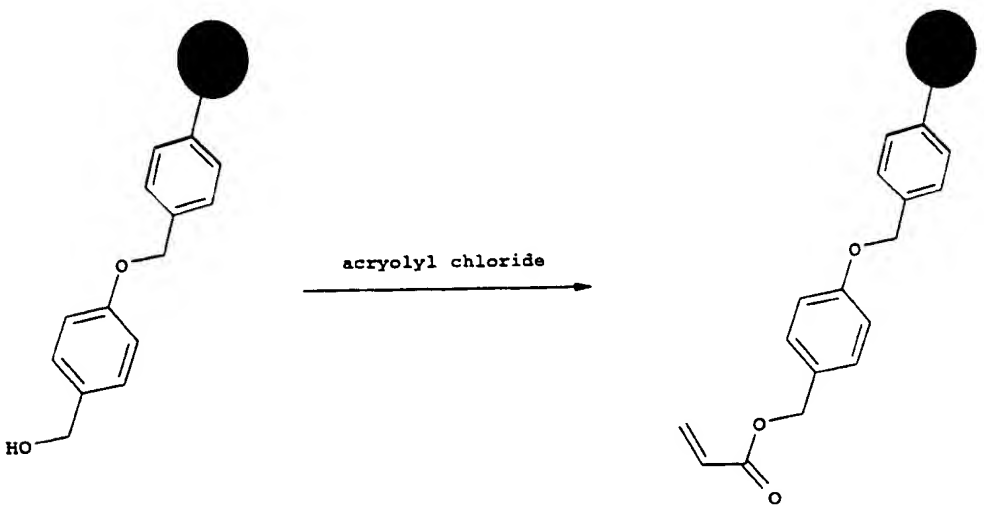
Thus, for example, compounds of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the Y moiety within one of X^3, X^4 and X^5 is carboxy, may be prepared by hydrolysis of esters of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the Y moiety within one of X^3, X^4 and X^5 is $-CO_2R^{12}$ group (in which R^{12} is alkyl, alkenyl or arylalkyl). The hydrolysis may conveniently be carried out by alkaline hydrolysis using a base, such as an alkali metal hydroxide, e.g. lithium hydroxide, or an alkali metal carbonate, e.g. potassium carbonate, in the presence of an aqueous/organic solvent mixture, using organic solvents such as dioxan, tetrahydrofuran or methanol, at a temperature from about ambient to about reflux. The hydrolysis of the esters may also be carried out by acid hydrolysis using an inorganic acid, such as hydrochloric acid, in the presence of an aqueous/inert organic solvent mixture, using organic solvents such as dioxan or tetrahydrofuran, at a temperature from about 50°C to about 80°C.

As another example compounds of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefor defined, and where the Y moiety within one of X^3, X^4 and X^5 is carboxy, may be prepared by acid catalysed removal of the tert-butyl group of tert-butyl esters of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the Y moiety within one of X^3, X^4 and X^5 is $-CO_2R^{12}$ (in which R^{12} is $-CO_2{}^tBu$), using standard reaction conditions.

In a process A compounds of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the Y moiety within one of X^3, X^4 and X^5 is carboxy, may be prepared by coupling of an acid (or an acid halide) with an amine to give an amide bond within R^3 using standard peptide coupling procedures as described hereinafter.

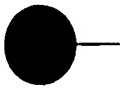
As an example of process A, compounds of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the Y moiety within one of X^3, X^4 and X^5 is carboxy, may be prepared by:-

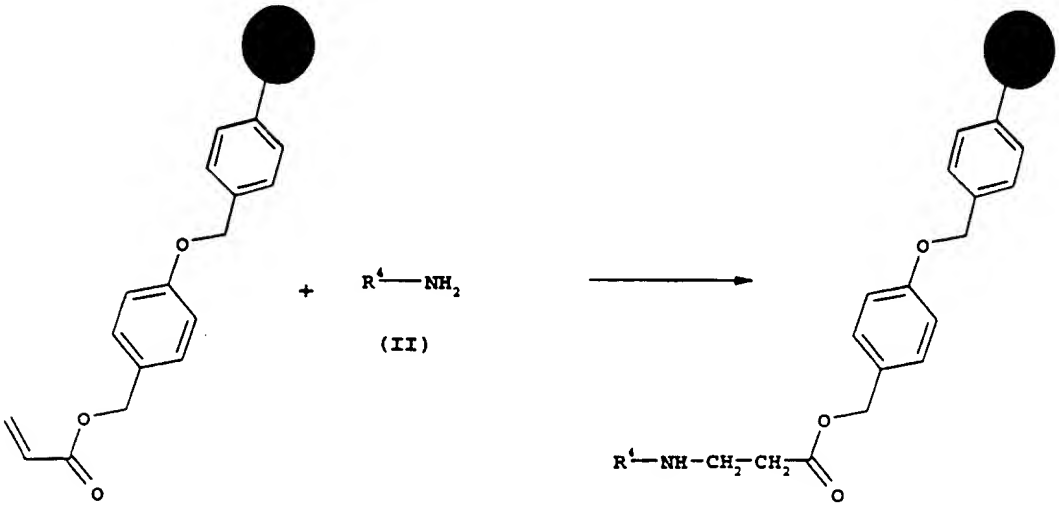
(i) treating Wang resin (4-hydroxymethylphenoxylated styrene/divinylbenzene copolymer) with acryloyl chloride, in the presence of a tertiary amine, such as diisopropylethylamine, in an inert solvent, such as dichloromethane, at a temperature at about room temperature, to give Resin A:



(Wang Resin) (Resin A)

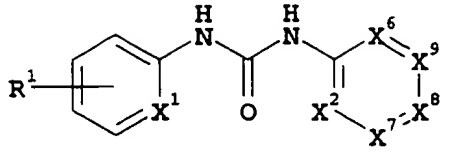
where  represents the polymeric core comprising polystyrene crosslinked with 1% to 2% divinylbenzene.

(ii) reaction of Resin A with amines of formula (II), wherein R^4 is as defined hereinbefore, in the presence of a base, such as a tertiary organic base, for example diisopropylethylamine, in dimethylformamide and at a temperature at about room temperature, to give Resin 1, in which R^4 and  are as defined hereinbefore:



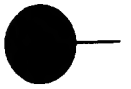
(Resin A) (Resin 1)

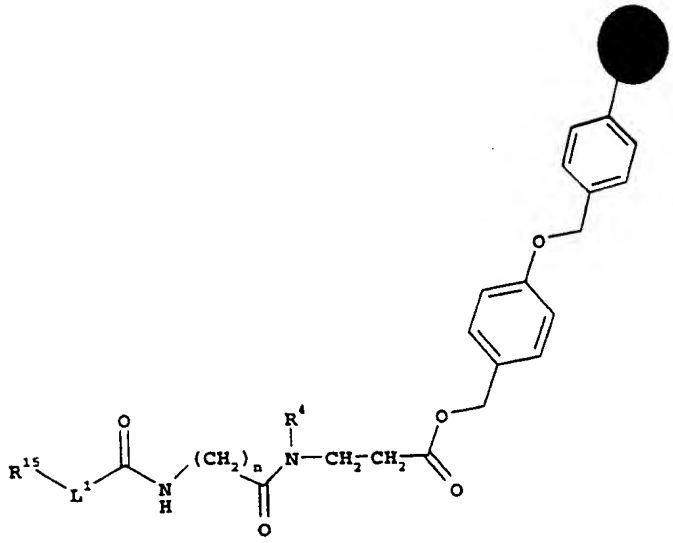
(iii) reaction of Resin 1 with compounds of formula (III)



(III)

wherein R^1, X^1, X^2 and X^6 are as hereinbefore defined, one of X^7, X^8 and X^9 represents CR^{14} [in which R^{14} is $-L^1-(CH_2)_n-CO_2H$ (in which L^1 and n are as

hereinbefore defined)], and the others independently represent N or CR^2 (in which R^2 is as hereinbefore defined), in the presence of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and diisopropylethylamine in dimethylformamide, at room temperature, to give resin 2 wherein R^4, R^9, n and  are as hereinbefore defined and R^{15} represents a monovalent radical derived from (III) in which R^1, X^1, X^2 and X^6 are as hereinbefore defined, one of X^7, X^8 and X^9 represents CH and the others independently represent N or CR^2 (in which R^2 is as hereinbefore defined) by removing one of the hydrogen atoms from X^7, X^8 or X^9:

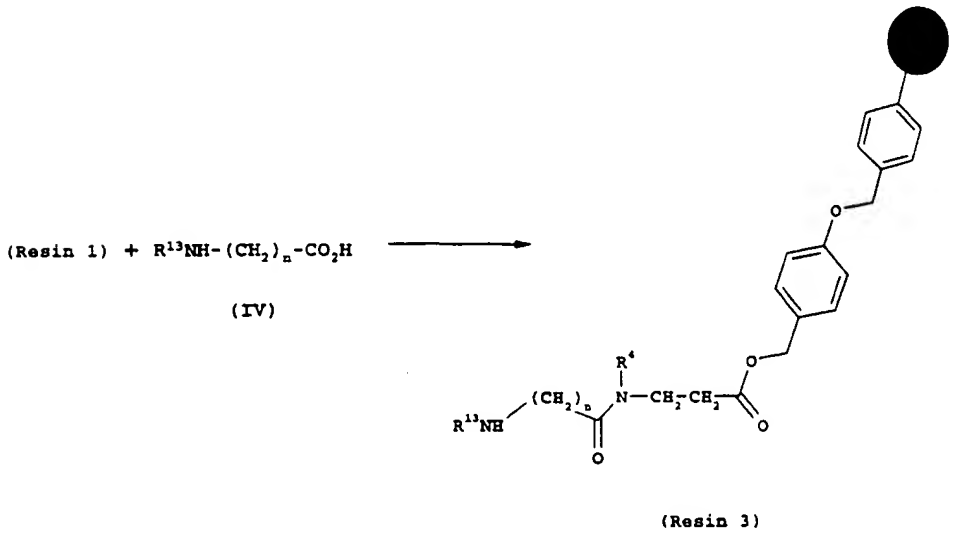


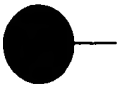
(Resin 2)

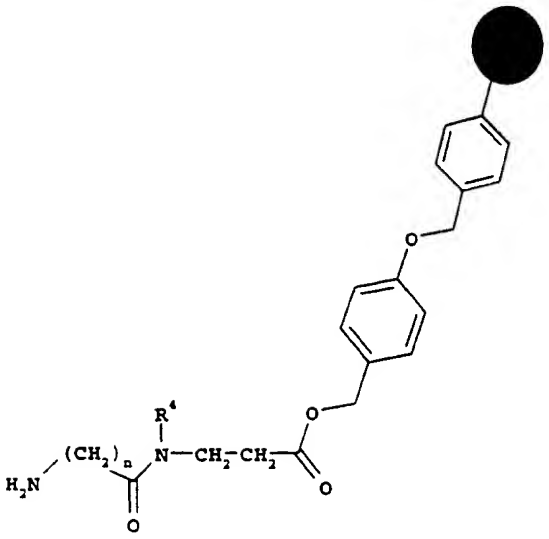
(iv) Resin 2 may then be treated with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

As another example of process A, compounds of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the L^1 and Y moieties within one of X^3, X^4 and X^5 are $-R^9-C(=O)-NH-$ (where R^9 is as hereinbefore defined) and carboxy respectively, may be prepared by:-

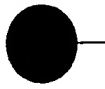
(i) treating Resin 1, wherein R^4 and  are as hereinbefore defined, with a suitably protected amino-acid of formula (IV), wherein R^{13} is a suitable amino protecting group (such as 9-fluorenylmethoxycarbonyl, FMOC) and n is as hereinbefore defined, in the presence of O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and diisopropylethylamine in dimethylformamide, at room temperature to give Resin 3, wherein R^4 and  are as hereinbefore defined:

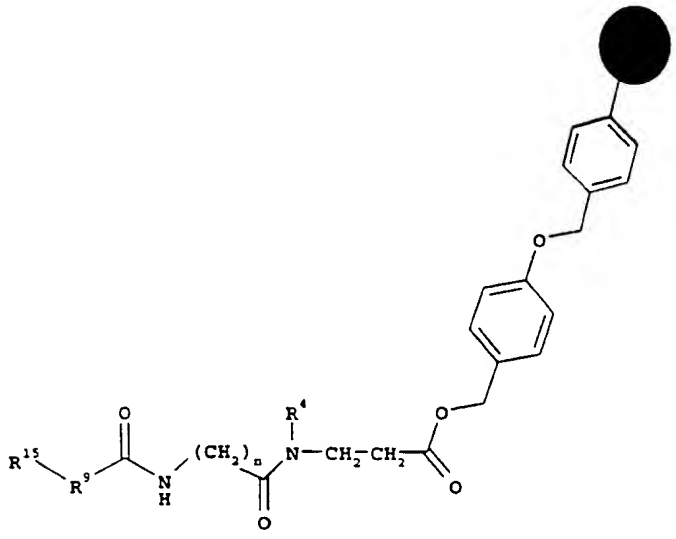


(ii) The resulting Resin 3, may then be deprotected, for example by treating with piperidine in dimethylformamide, at room temperature, to give Resin 4, wherein R^4, n and  are as hereinbefore defined:



(Resin 4)

(iii) Resin 4 may then be treated with compounds of general formula (III), wherein R^1, X^1, X^2 and X^6 are as hereinbefore defined, one of X^7, X^8 and X^9 represents CR^{14} [in which R^{14} is $-R^9-CO_2H$ (where R^9 is as hereinbefore defined)], and the others independently represent N or CR^2 (in which R^2 is as hereinbefore defined), using standard peptide coupling procedures, for example those described hereinabove, to give resin 5, wherein R^4, R^9, R^{15}, n and  are as hereinbefore defined:

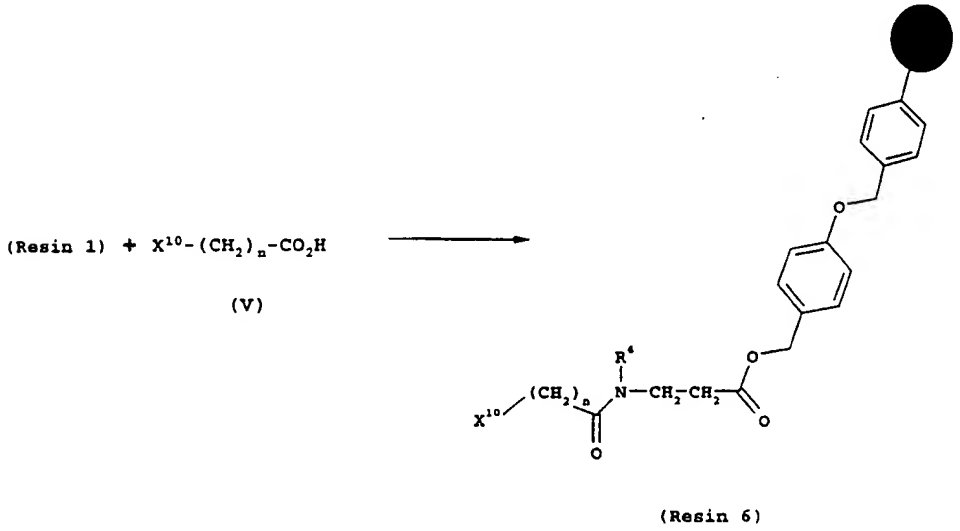


(Resin 5)

(iv) Resin 5 may then be treated with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

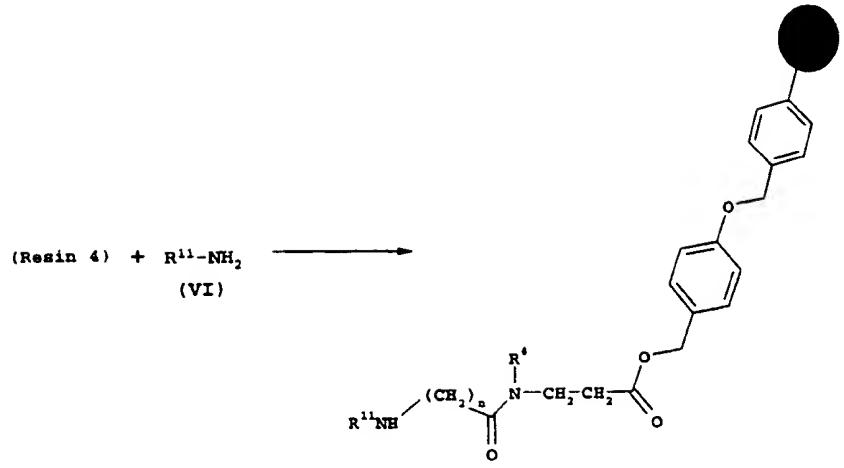
As another example of process A, compounds of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the L^1 and Y moieties within one of X^3, X^4 and X^5 are $-R^9-C(=O)-(NR^{11})-$ (where R^9 and R^{11} is as hereinbefore defined) and carboxy respectively, may be prepared by:-

(i) treating Resin 1, wherein R^4 and  are as hereinbefore defined, with compounds of formula (V), wherein n is as hereinbefore defined and X^{10} is a halogen atom, preferably bromine, using standard peptide coupling procedures, for example those described hereinabove, to give Resin 6:



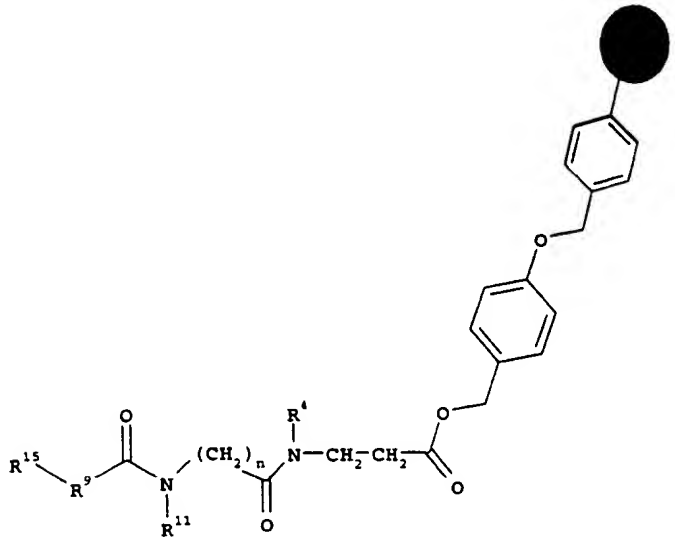
(Resin 6)

(ii) Reaction of Resin 6 with amines of formula (VI), wherein R^{11} is as hereinbefore defined, in an inert solvent such as dimethyl sulphoxide, and at a temperature at about 80°C. to give Resin 7, wherein R^4, R^{11}, n and  are as hereinbefore defined:



(Resin 7)

(iii) Resin 7 may then be treated with compounds of general formula (III), wherein R^1, X^1, X^2 and X^6 are as hereinbefore defined, one of X^7, X^8 and X^9 represents CR^{14} [in which R^{14} is $-R^9-CO_2H$ (where R^9 is as hereinbefore defined)], and the others independently represent N or CR^2 (in which R^2 is as hereinbefore defined), using standard peptide coupling procedures, for example those described hereinabove, to give resin 8 wherein R^4, R^9, R^{11}, R^{15}, n and  are as hereinbefore defined:



(Resin 8)

(iv) Resin 8 may then be treated with trifluoroacetic acid in an inert solvent such as dichloromethane and at a temperature at about room temperature.

Esters of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined and where Y moiety within one of X^3, X^4 and X^5 is a $-CO_2R^{12}$ group (in which R^{12} is as hereinbefore defined), may be prepared by reaction of compounds of formula (III), wherein R^1, X^1, X^2 and X^6 are as hereinbefore defined, one of X^7, X^8 and X^9 represents C-R^{14} [in which R^{14} is $-L^1-(CH_2)_n-C(=O)X^{11}$ (where L^1 and n are as hereinbefore defined and X^{11} is a hydroxy group, or a halogen, preferably chlorine, atom)] and the others independently represent N or CR^2 (where R^2 is as hereinbefore defined), with amines of formula (VII):-

$$R^4\text{-HN-}CH_2\text{-}CH_2\text{-}CO_2R^{12} \qquad \text{(VII)}$$

wherein R^4 and R^{12} are as hereinbefore defined. When X^{11} is a hydroxy group the reaction may be carried out using standard peptide coupling procedures as described hereinbefore. When X^{11} is a halogen atom the reaction may be carried out with the aid of a base, such pyridine, preferably in a solvent such as tetrahydrofuran and at a temperature at about room temperature.

According to a further process B compounds of the invention may be prepared by interconversion of other compounds of the invention.

For example compounds of formula (I) wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the Y moiety within one of X^3, X^4 and X^5 is -C(=O)-NHOH, may be prepared by reaction of compounds of formula (I), wherein R^1, X^1, X^2, X^3, X^4, X^5 and X^6 are as hereinbefore defined, and where the Y moiety within one of X^3, X^4 and X^5 is carboxy, with hydroxylamine using standard peptide coupling procedures such as treatment with a carbodiimide, for example dicyclohexylcarbodiimide, in the presence of triethylamine, in an inert solvent such as dichloromethane or tetrahydrofuran and at a temperature at about room temperature. The coupling may also be carried out using 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide in dichloromethane at room temperature. The preparation may also be carried out using an O-protected hydroxylamine such as

O-(trimethylsilyl)hydroxylamine, O-(t-butyldimethylsilyl)-hydroxylamine, or O-(tetrahydropyranyl)hydroxylamine followed by treatment with acid.

As another example of the interconversion process, compounds of formula (I) containing sulphoxide linkages may be prepared by the oxidation of corresponding compounds containing -S- linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature, or alternatively by means of potassium hydrogen peroxomonosulphate in a medium such as aqueous methanol, buffered to about pH5, at temperatures between about 0°C and room temperature. This latter method is preferred for compounds containing an acid-labile group.

As another example of the interconversion process, compounds of formula (I) containing sulphone linkages may be prepared by the oxidation of corresponding compounds containing -S- or sulphoxide linkages. For example, the oxidation may conveniently be carried out by means of reaction with a peroxyacid, e.g. 3-chloroperbenzoic acid, preferably in an inert solvent, e.g. dichloromethane, preferably at or near room temperature.

It will be appreciated that compounds of the present invention may contain asymmetric centres. These asymmetric centres may independently be in either the R or S configuration. It will be apparent to those skilled in the art that certain compounds of the invention may also exhibit geometrical isomerism. It is to be understood that the present invention includes individual geometrical isomers and stereoisomers and mixtures thereof, including racemic mixtures, of compounds of formula (I) hereinabove. Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallisation techniques, or they are separately prepared from the appropriate isomers of their intermediates.

According to a further feature of the invention, acid addition salts of the compounds of this invention may be prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention may be prepared either by dissolving the free base in water or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, e.g. aqueous sodium bicarbonate solution or aqueous ammonia solution.

Compounds of this invention can be regenerated from their base addition salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, e.g. hydrochloric acid.

Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxan, tetrahydrofuran or methanol.

According to a further feature of the invention, base addition salts of the compounds of this invention may be prepared by reaction of the free acid with the appropriate base, by the application or adaptation of known methods. For example, the base addition salts of the compounds of this invention may be prepared either by dissolving the free acid in water or aqueous alcohol solution or other suitable solvents containing the appropriate base and isolating the salt by evaporating the solution, or by reacting the free acid and base in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The starting materials and intermediates may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

Compounds of formula (III), wherein R^1, X^1, X^2 and X^6 are as hereinbefore defined, one of X^7, X^8 and X^9 represents C-R^{14} (in which R^{14} is as described hereinabove, or a suitably protected derivative thereof) and the others independently represent N or CR^{10} (where R^{10} is as hereinbefore defined), may be prepared by the application or adaptation of methods described in prepared as described in the specification of International Patent Application Publication No. WO 96/22966.

Intermediates of formulae (Resin 1), (Resin 2), (Resin 3), (Resin 4), (Resin 5), (Resin 6), (Resin 7) and (Resin 8) are novel compounds and, as such, they and their processes described herein for their preparation constitute further features of the present invention.

The present invention is further Exemplified but not limited by the following illustrative Examples and Reference Examples.

In the nuclear magnetic resonance spectra (NMR) the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances: s = singlet; d = doublet; t = triplet; m = multiplet; dd = doublet of doublets; b = broad.

Mass spectra (MS) were recorded on a Micromass Platform II mass spectrometer fitted with an Electrospray source and an HP1100 liquid chromatograph; using a mixture of acetonitrile and water (1:1, v/v) as the mobile phase, a flow rate of 0.3 ml/minute, an injection volume of 20µl, a run time of 2.0 minutes, a scan range of 150 - 850 Daltons Positive/Negative, a scan time of 2.0 seconds, an ESI voltage of 3.5Kv, an ESI pressure of 20n/m2 Nitrogen. Abbreviations have the following significances: w = weak.

EXAMPLE 1

Compounds A, B and C

A solution of ({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetic acid [0.80g, Reference Example 1] and 3-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-ylamino]-propionic acid ethyl ester [0.51g, Reference Example 2(c)] in dimethylformamide (25ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] (0.80g) and diisopropylethylamine (0.75ml). After stirring at room temperature for 2 hours the reaction mixture was treated with water (100ml) then extracted three times with ethyl acetate. The combined organic extracts were washed with hydrochloric acid (1M) , then with brine, then dried over magnesium sulphate and then evaporated. The residual oil was subjected to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (25:1, v/v) to give 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid ethyl ester as a colourless oil (0.76g). The ester was dissolved in tetrahydrofuran (50ml) and then treated with lithium hydroxide hydrate (0.065g) in water (10ml). After stirring at room temperature for 2 hours the mixture was concentrated to remove the tetrahydrofuran. The residual aqueous residue was washed with ethyl acetate then acidified by addition of hydrochloric acid (1M) and then extracted three times

with dichloromethane. The combined organic extracts were washed with brine, then dried over magnesium sulphate and then evaporated to give 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid as a white solid (0.58g, Compound A), m.p.73-76°C. [Elemental analysis:- C,60.69; H,6.85; N,11.79%. Calculated for $C_{30}H_{39}N_5O_7 \cdot 0.67H_2O$:- C,60.69; H,6.69; N,11.58%]. MS: 580 $[MH]^+$. HPLC: R_T=9.72 minutes (gradient elution using a mixture of acetonitrile and water 1:4 to 4:1).

(b) By proceeding in a manner similar to Example 1(a) but using 3-(3-imidazol-1-yl-prop-1-ylamino)-propionic acid ethyl ester [Reference Example 2(b)] there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(3-imidazol-1-yl)-prop-1-yl]-amino}-propionic acid as a white solid (Compound B), m.p. 58-62°C. MS: 563 $[MH]^+$. HPLC: R_T=9.70 minutes (gradient elution using a mixture of acetonitrile and water 1:4 to 4:1).

(c) By proceeding in a manner similar to Example 1(a) but using 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester [Reference Example 2(a)] there was prepared 3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid as a white solid (Compound C), m.p. 104-106°C. [Elemental analysis:- C,62.19; H,6.43; N,8.94% Calculated for $C_{32}H_{38}N_4O_8 \cdot 0.67H_2O$:- C,62.13; H,6.40; N,9.05%]. MS: 605 $[MH]^+$. HPLC: R_T=11.92 minutes (gradient elution using a mixture of acetonitrile and water 1:4 to 4:1).

EXAMPLE 2

Compounds D to BU

Step 1. Wang resin (3.0g, 0.92mmol/g) was allowed to swell in dichloromethane (30ml) for 15 minutes, then treated with diisopropylethylamine (1.8ml) followed by acryloyl chloride (0.9ml). The mixture was kept at room temperature for 3 hours with occasional gentle shaking then filtered to give resin A which was washed (i) three times with dichloromethane (15ml), (ii) three times with methanol (15ml), (iii) three times with dimethylformamide (15ml), (iv) three times with methanol (15ml), (v) three times with dichloromethane (15ml) and then dried in a desiccator under high vacuum for 2 hours.

Step 2. Resin A (40mg) was placed in a Jones tube, suspended in dimethylformamide (1ml) and then treated with 1-(3-aminoprop-1-yl)-2-pyrrolidinone (50mg). After standing at room

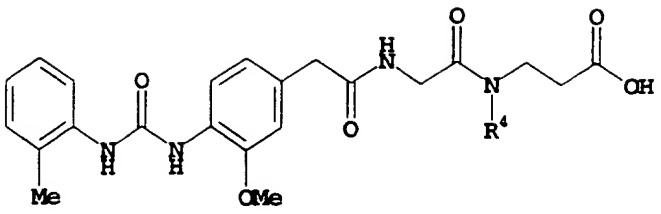
temperature for 90 minutes the mixture was filtered to give resin B which was washed (i) four times with dimethylformamide (5ml), (ii) three times with methanol (5ml), (iii) dimethylformamide (5ml).

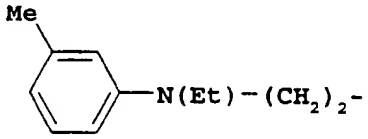
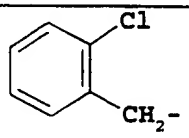
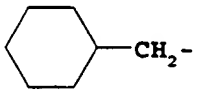
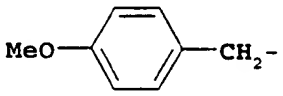
Step 3. Resin B from step 2 was treated with a solution of ({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino]-acetic acid (30mg, Reference Example 3) in dimethyformamide (1ml), and then with a solution of [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] (30mg) in dimethylformamide (1ml) and diisopropylethylamine (30μl). After standing at room temperature for 3 hours with occasional agitation the mixture was filtered to give resin C which was washed (i) four times with dimethylformamide (5ml), (ii) three times with methanol(5ml), (iii) four times with dichloromethane (45ml) and then dried in a desiccator under vacuum for 2 hours.

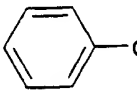
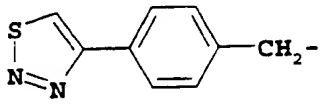
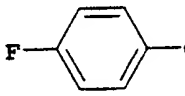
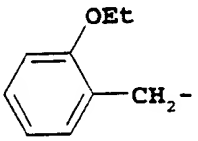
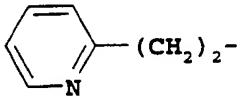
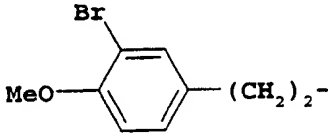
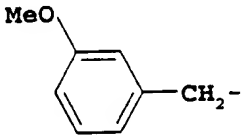
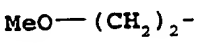
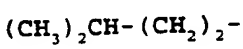
Step 4. Resin C from step 3 was treated with a mixture of dichloromethane and trifluoroacetic acid (2ml, 1:1 v/v). After standing at room temperature for 45 minutes the mixture was filtered, and the resin was washed with dichloromethane. The combined filtrate and washings were evaporated to give 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid (Compound D). MS: 568 $[MH]^+$. HPLC: R_T=3.11 minutes, area of main peak as a percentage of the total sample =96% (gradient elution using a mixture of acetonitrile and water 3:7 to 17:3 v/v).

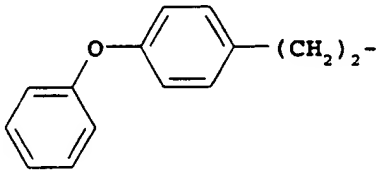
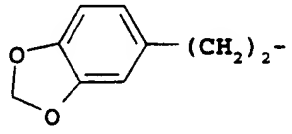
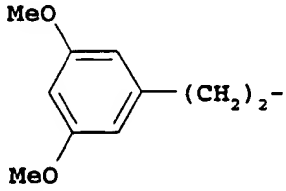
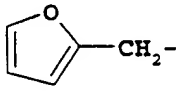
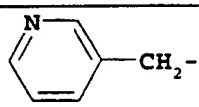
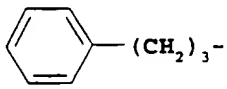
By proceeding in a similar manner to Example 2, but using the appropriately substituted amines in step 2, there were prepared Compounds E to BU depicted in Table 1.

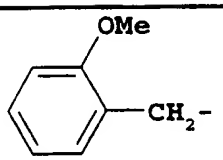
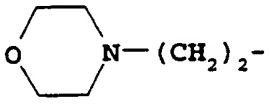
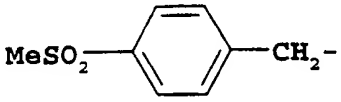
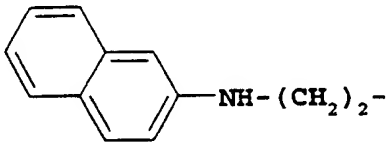
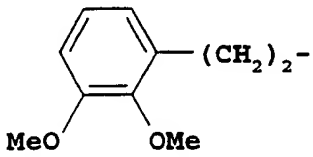
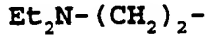
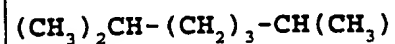
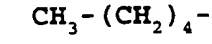
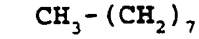
Table 1

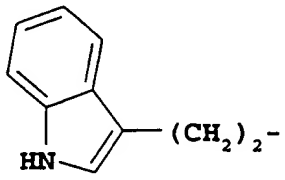
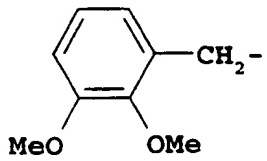
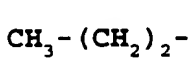
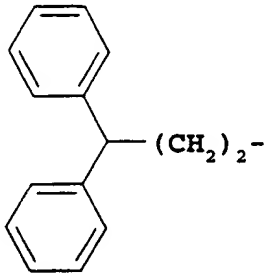
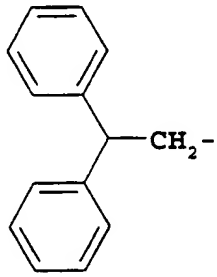
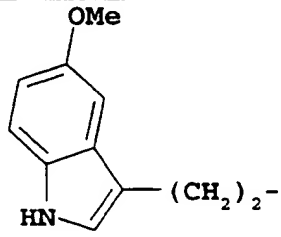
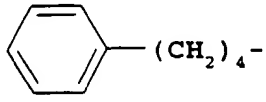
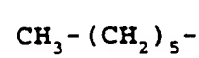


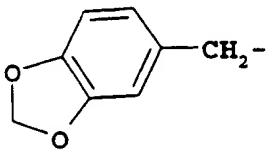
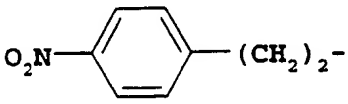
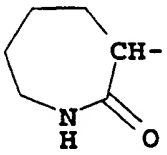
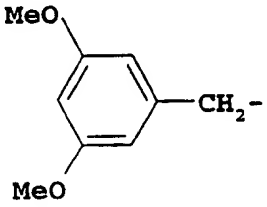
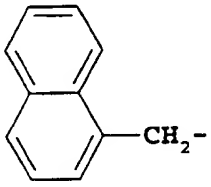
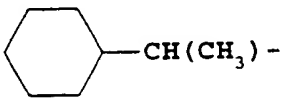
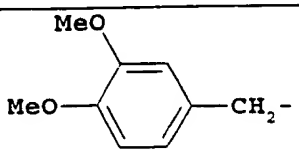
Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound E		C33H41N5O6	4.5, 95%	604	
Compound F	$CH_3C(=O)NH-(CH_2)_2-$	C26H33N5O7	2.7, 86%	528	526
Compound G		C29H31ClN4O6	5.4, 93%	567	565
Compound H	$MeO-(CH_2)_3-$	C26H34N4O7	3.6, 96%	515	513
Compound I		C29H38N4O6	5.7, 98%	539	537
Compound J		C30H34N4O7	5.0, 85%	563	561
Compound K	$(CH_3)_2CH-CH_2-$	C26H34N4O6	4.6, 92%	499	497

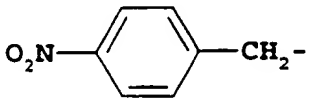
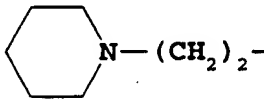
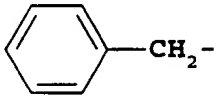
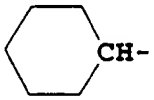
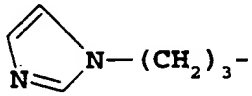
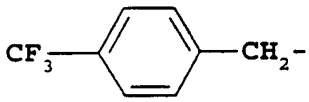
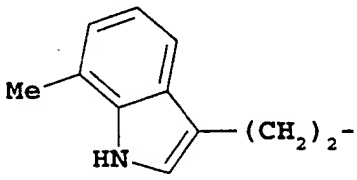
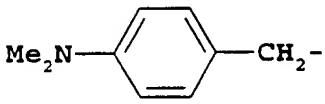
Compound L		C30H34N4O6	5.2, 82%	547w	545
Compound M		C31H32N6O6S	7.7, 60%	617w	615
Compound N		C30H33FN4O6	8.0, 81%	565	563
Compound O		C31H36N4O7	5.6, 97%		
Compound P		C29H33N5O6	2.7, 96%	548	546
Compound Q		C31H35N4BrO7	5.8, 95%	657	655
Compound R		C30H34N4O7	5.0, 89%	563	561
Compound S		C25H32N4O7	3.5, 94%	499	501
Compound T		C27H36N4O6	5.2, 90%	513	511

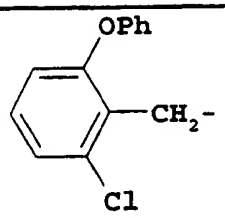
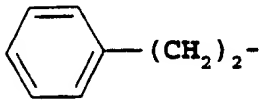
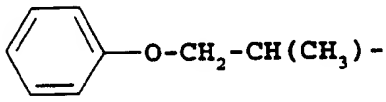
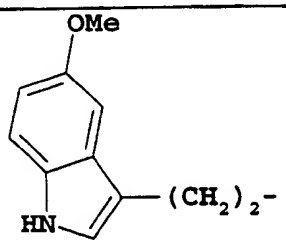
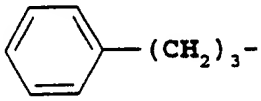
Compound U		C36H38N4O7	7.0, 86%	639	637
Compound V		C31H34N4O8	7.8, 68%	591	589
Compound W	$CH_3-(CH_2)_3-$	C26H34N4O6	4.7, 97%	499	497
Compound X		C32H38N4O8	5.4, 88%	607	605
Compound Y		C27H30N4O7	4.5, 95%	523	521
Compound Z	$CH_2=CH-CH_2-$	C25H30N4O6	3.9, 97%	483	481
Compound AA		C28H31N5O6	2.6, 95%	534	532
Compound AB	$Cl-(CH_2)_3-$	C25H31ClN4O6	4.5, 95%	519	517
Compound AC		C31H36N4O6	5.7, 88%	561	559

Compound AD		C30H34N4O7	5.1, 83%	563	561
Compound AE		C28H37N5O7	2.6, 91%	556	554
Compound AF		C30H34N4O8S	6.4, 76%	611	609
Compound AG		C23H28N4O6	3.2, 89%		455
Compound AH		C34H37N5O6	5.9, 97%	612	610
Compound AI		C32H38N4O8	5.3, 96%	607	605
Compound AJ		C28H39N5O6	3.0, 96%	542	540
Compound AK		C30H42N4O6	5.3, 96%	555	553
Compound AL		C27H36N4O6	5.2, >90%	513	511
Compound AM		C30H42N4O6	7.4, 93%	555	553

Compound AN		C32H35N5O6	5.1, 67%	586	584
Compound AO		C31H36N4O8	7.6, 79%	593	591
Compound AP		C25H32N4O6	4.1, 98%	485	483
Compound AQ		C37H40N4O6	6.9, 96%	637	635
Compound AR		C36H38N4O6	6.4, 96%	623	621
Compound AS		C33H37N5O7	5.0, 82%	616	614
Compound AT		C32H38N4O6	6.2, 95%	575	573
Compound AU		C28H38N4O6	6.0, >90%	527	525

Compound AV		C30H32N4O8	4.9, 88%	577	575
Compound AW	$CH_3C(=O)NH-(CH_2)_2-$	C26H33N5O7	1.8, 67%	528	526
Compound AX		C30H33N5O8	7.9, 74%	592	590
Compound AY		C28H35N5O7	3.3, >95%	554	552
Compound AZ		C31H36N4O8	5.2, 76%	593	591
Compound BA	$Me_2N-(CH_2)_3-$	C27H37N5O6	2.6, 93%	528	526
Compound BB		C33H34N4O6	6.0, 74%	583	581
Compound BC		C30H40N4O6	6.0, 95%	553	552
Compound BD		C31H36N4O8	4.7, 87%	593	591

Compound BE	$Et_2N-(CH_2)_2-$	C28H39N5O6	1.9, 83%	542	540
Compound BF		C29H31N5O8	7.7, 76%	578	576
Compound BG		C29H39N5O6	3.1, 97%	554	552
Compound BH		C29H32N4O6	5.0, 96%	533	531
Compound BI		C28H36N4O6	5.0, 97%	525	523
Compound BJ	$(CH_3)_2CH-CH_2-$	C26H34N4O6	4.6, 95%	499	497
Compound BK		C28H34N6O6	2.6, 98%	551	549
Compound BL		C30H31F3N4O6	6.0, 83%	601	599
Compound BM	$MeO-(CH_2)_2-$	C25H32N4O7	3.5, 91%	501	499
Compound BN		C33H37N5O6	8.6, 58%		598
Compound BO		C31H37N5O6	1.8, 83%	576	574
Compound BP	$(CH_3)_2-CH-$	C25H32N4O6	3.9, 95%	485	483

Compound BQ		C35H35ClN4O7	6.7, 88%	659	657
Compound BR		C30H34N4O6	5.2, 93%	547	545
Compound BS		C31H36N4O7	5.5, 88%	577	575
Compound BT		C33H37N5O7	8.0, 52%		614
Compound BU		C31H36N4O6	8.4, 85%	561	559

EXAMPLE 3

Compounds BV to FJ

Step 1. Resin B from Step 2 Example 2 was treated with bromoacetic acid (0.47g) in dimethylformamide (7ml) and diisopropylcarbodiimide (0.67ml). After standing at room temperature for 1.5 hours the mixture was filtered to give resin D which was washed.

Step 2. Resin D (100mg) was swelled with dimethyl sulphoxide (1.5ml) and then treated with propylamine (10 equivalents). After heating for 2 hours at 80°C the mixture was filtered to give resin E which was washed (i) three times with dimethylformamide, (ii) three times with tetrahydrofuran, (iii) three times with dichloromethane.

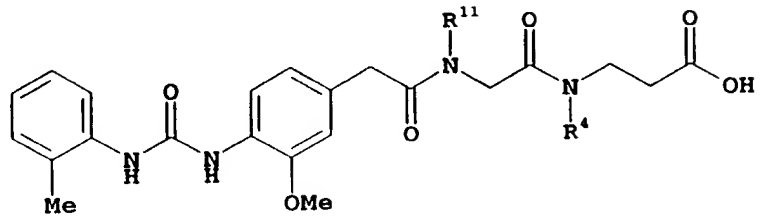
Step 3. Resin E was treated with a solution of [3-methoxy-4-(3-o-tolylureido)phenyl]-acetic acid (70 mg, Reference Example 5) in dimethylformamide (1ml), a solution of [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] (75 mg) in dimethylformamide (1ml), and diisopropylethylamine (100µl). After standing at room temperature for 2 hours with

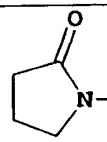
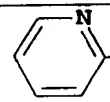
occasional agitation the mixture was filtered to give resin F which was washed (i) four times with dimethylformamide, (ii) three times with methanol, (iii) three times with dichloromethane and then dried under vacuum.

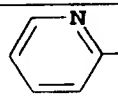
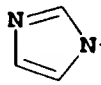
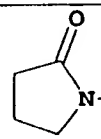
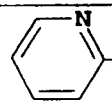
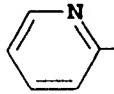
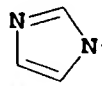
Step 4. Resin F was treated with a mixture of dichloromethane and trifluoroacetic acid (2ml, 1:1 v/v) and allowed to stand for 45 minutes. The mixture was filtered and the resin was washed with dichloromethane. The combined filtrate and washings were evaporated to give 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-prop-1-ylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid (Compound BV).

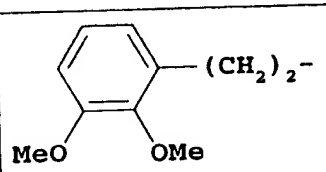
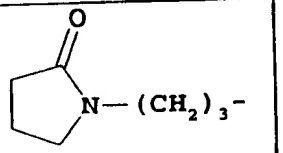
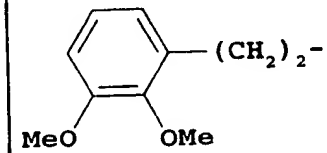
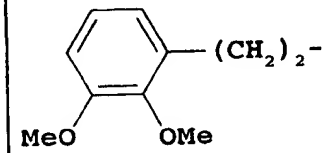
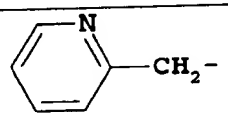
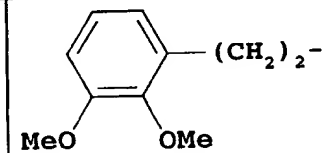
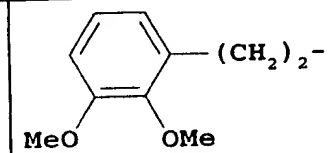
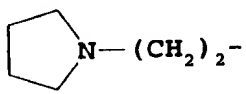
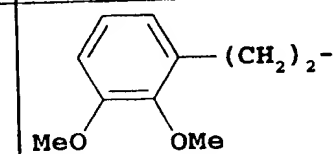
By proceeding in a similar manner to Example 3, but using the appropriately substituted amines in step 1 and the appropriately substituted amines step 3, there were prepared Compounds BW to FJ depicted in Table 2.

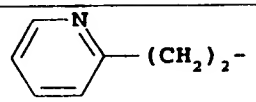
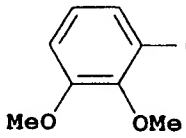
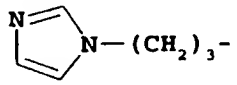
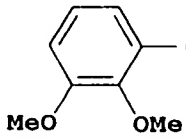
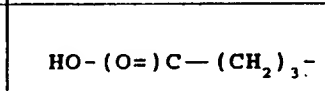
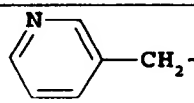
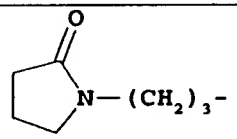
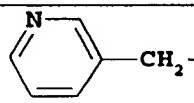
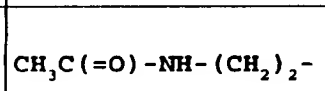
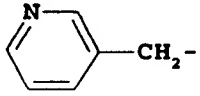
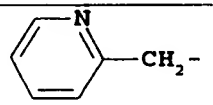
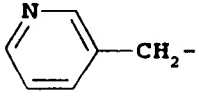
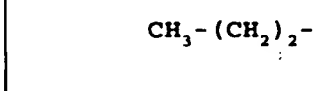
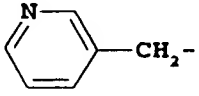
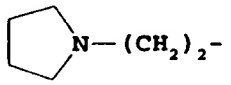
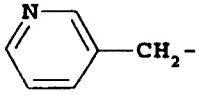
Table 2

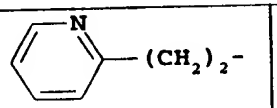
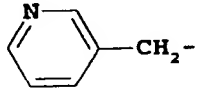
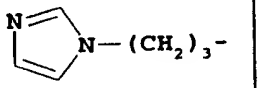
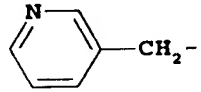
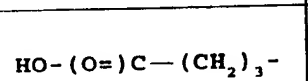
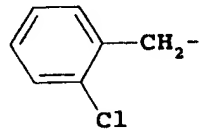
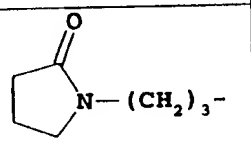
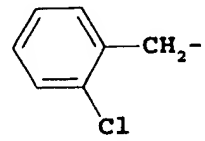
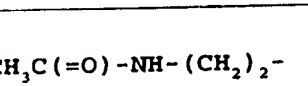
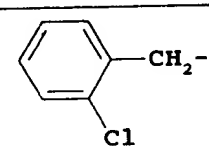
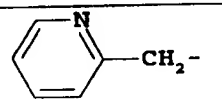
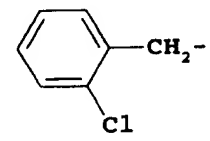
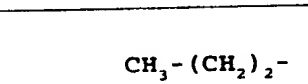
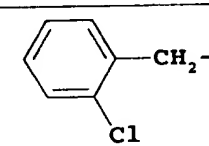


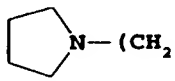
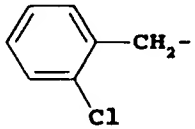
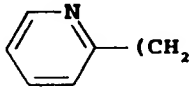
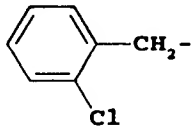
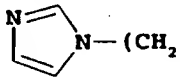
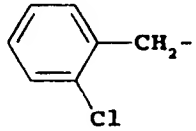
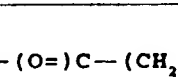
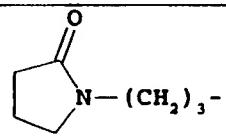
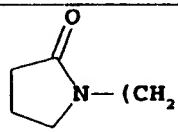
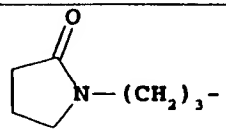
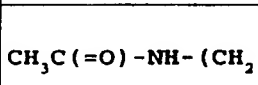
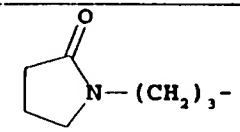
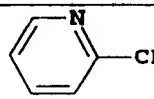
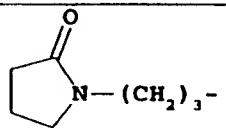
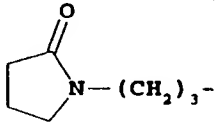
Compound Number	R^{11}	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound BW		$CH_2=CH-CH_2-$	C32H41N5O7	2.7, 80%	625 $(M+18)^+$	
Compound BX	$CH_3C(=O)-NH-(CH_2)_2-$	$CH_2=CH-CH_2-$	C29H37N5O7	2.5, 78%	568	
Compound BY		$CH_2=CH-CH_2-$	C31H35N5O6	2.8, 68%	574	
Compound BZ	$CH_3-(CH_2)_2-$	$CH_2=CH-CH_2-$	C28H36N4O6	6.7, 100%	542 $[M+18]^+$	
Compound CA		$CH_2=CH-CH_2-$	C31H41N5O6	2.0, 100%	580	

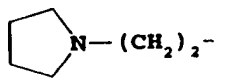
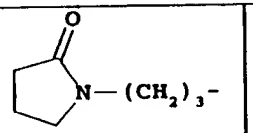
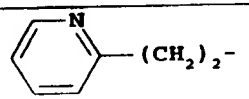
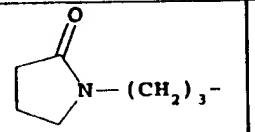
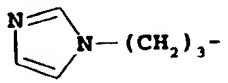
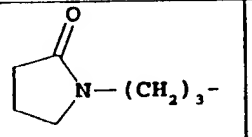
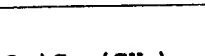
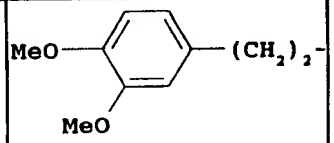
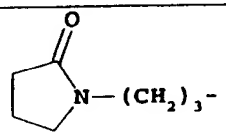
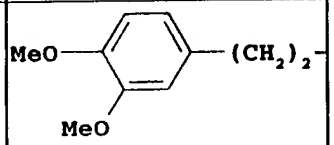
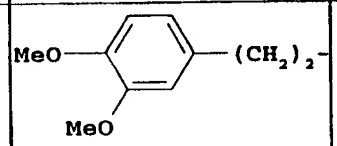
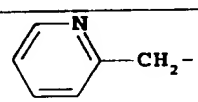
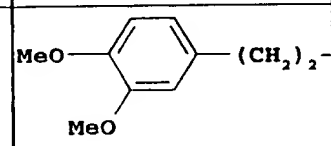
Compound CB		$CH_2=CH-CH_2-$	C32H37N5O6	3.5, 40%	588	
Compound CC		$CH_2=CH-CH_2-$	C31H38N6O6	3.0, 95%	591	
Compound CD		$CH_3C(=O)-NH-(CH_2)_2-$	C33H44N6O8	2.3, 77%		
Compound CE	$CH_3C(=O)-NH-(CH_2)_2-$	$CH_3C(=O)-NH-(CH_2)_2-$	C30H40N6O8	2.2, 79%	630 $[M+18]^+$	
Compound CF		$CH_3C(=O)-NH-(CH_2)_2-$	C32H38N6O7	2.4, 81%	619	
Compound CG	$CH_3-(CH_2)_2-$	$CH_3C(=O)-NH-(CH_2)_2-$	C29H39N5O7	1.8, 100%	570	
Compound CH		$CH_3C(=O)-NH-(CH_2)_2-$	C32H44N6O7	2.4, 81%	625	
Compound CI		$CH_3C(=O)-NH-(CH_2)_2-$	C33H40N6O7	2.3, 75%	633	
Compound CJ		$CH_3C(=O)-NH-(CH_2)_2-$	C32H41N7O7	2.2, 89%	636	

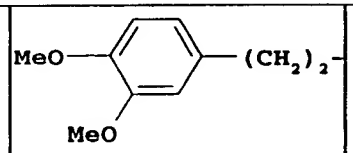
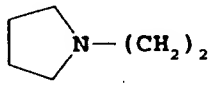
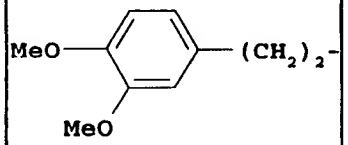
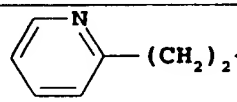
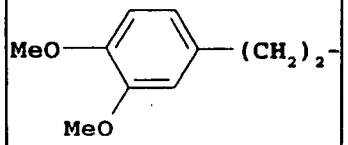
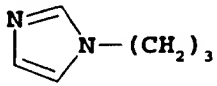
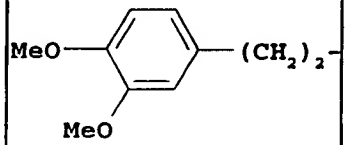
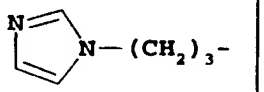
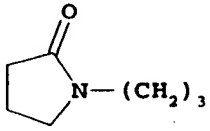
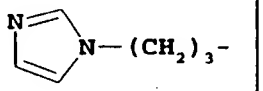
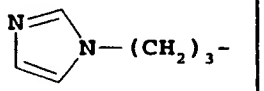
Compound CK	HO-(O=)C—$(CH_2)_3$-		C36H44N4O10	6.7, 100%	690	
Compound CL			C39H49N5O9	6.8, 100%	730	
Compound CM	$CH_3C(=O)$-NH-$(CH_2)_2$-		C36H45N5O9	6.3, 100%	689	
Compound CN			C38H43N5O8	6.8, 81%	698	
Compound CO	CH_3-$(CH_2)_2$-		C35H44N4O8	8.5, 100%	666 $[M+18]^+$	
Compound CP			C38H49N5O8	6.9, 100%	704	

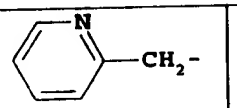
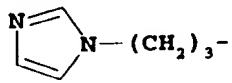
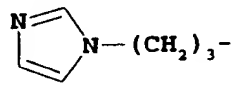
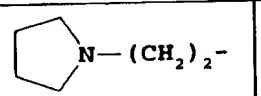
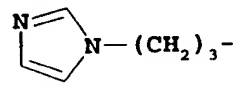
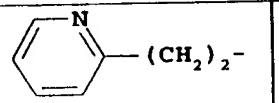
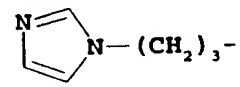
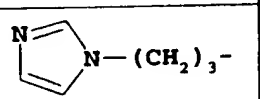
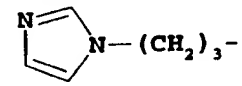
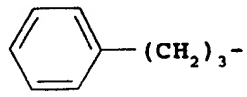
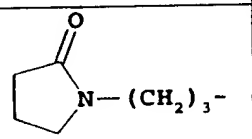
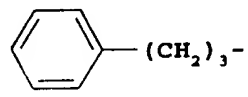
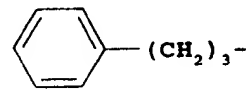
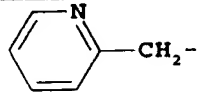
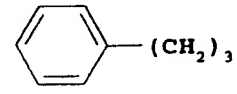
Compound CQ			C39H45N5O8	6.7, 89%	712	
Compound CR			C38H46N6O8	6.1, 69%	715	
Compound CS			C32H37N5O8	2.1, 22%	620	
Compound CT			C35H42N6O7	1.8, 82%		657
Compound CU			C32H38N6O7	2.2, 18%	619	
Compound CV			C34H36N6O6	2.2, 50%	625	
Compound CW			C31H37N5O6		576	
Compound CX			C34H42N6O6	2.1, 16%	631	

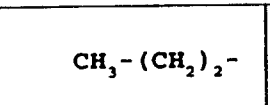
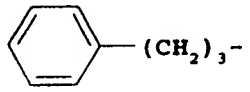
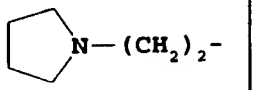
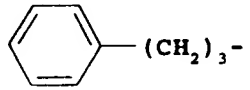
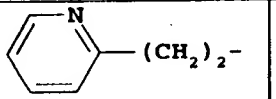
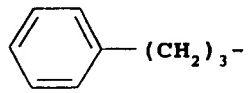
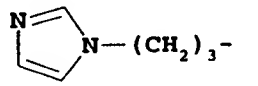
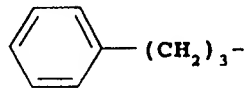
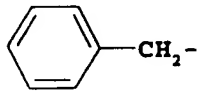
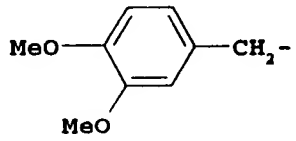
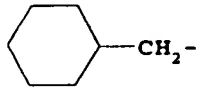
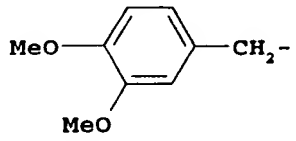
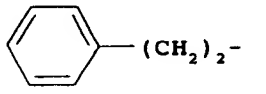
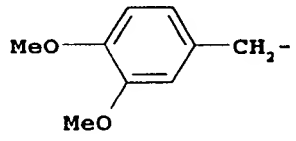
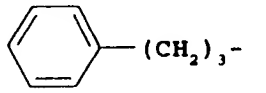
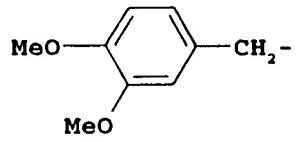
Compound CY			C35H38N6O6	2.1, 37%	639	
Compound CZ			C34H39N7O6	2.1, 40%	642	
Compound DA			C33H37ClN4O8	7.0, 100%		651
Compound DB			C36H42ClN5O7	7.0, 55%	709 $[M+18]^+$	
Compound DC			C33H38ClN5O7	6.6, 30% 2.6, 70%		650
Compound DD			C35H36ClN5O6	7.0, 62%	566	
Compound DE			C32H37ClN4O6	6.6, 64% 8.7, 46%	566	

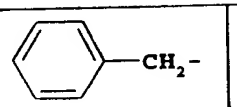
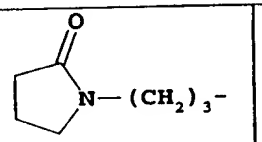
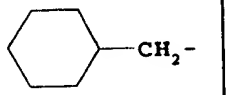
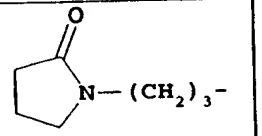
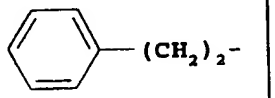
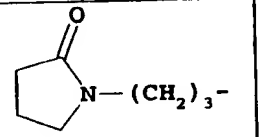
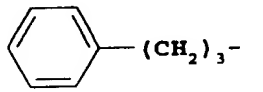
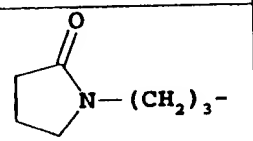
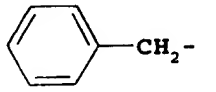
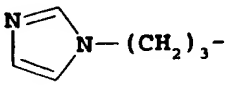
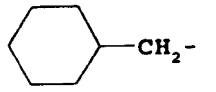
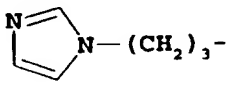
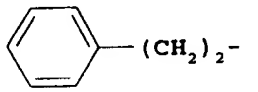
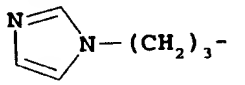
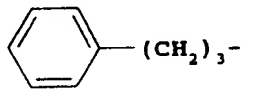
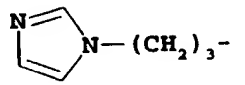
Compound DF			C35H42ClN5O6	7.0, 50%	664	
Compound DG			C36H38ClN5O6	6.8, 53%	672	
Compound DH			C35H39ClN6O6	6.4, 23%	675	
Compound DI			C33H43N5O9	2.5, 46%	612	652
Compound DJ			C36H48N6O8	2.5, 67%	710 $[M+18]^+$	
Compound DK			C33H44N6O8	2.3, 86%	670 $[M+18]^+$	
Compound DL			C35H42N6O7	2.6, 67%	659	
Compound DM			C32H43N5O7	2.0, 61%	627	

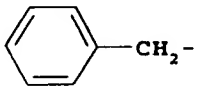
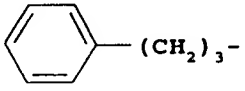
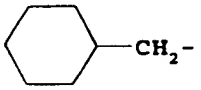
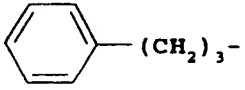
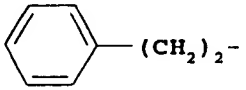
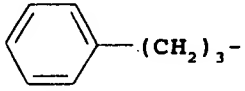
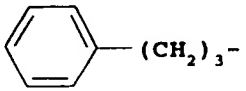
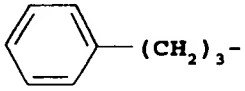
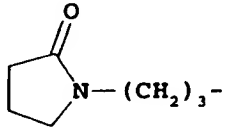
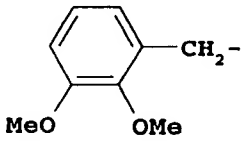
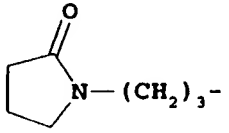
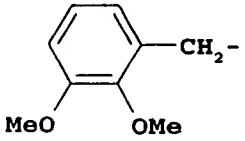
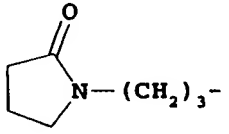
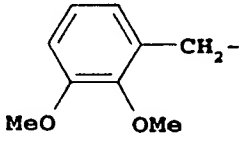
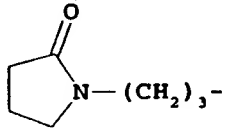
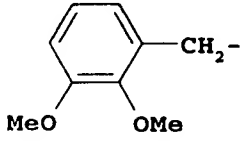
Compound DN			C35H48N6O7	2.6, 72%	665	
Compound DO			C36H44N6O7	2.5, 67%	673	
Compound DP			C35H45N7O7	5.4, 76%	676	
Compound DQ			C35H42N4O10	5.5, 30%	612	
Compound DR			C38H47N5O9	5.4, 67%	701	
Compound DS			C35H43N5O9	2.2, 100%	678	
Compound DT			C37H41N5O8	5.5, 53%	684	

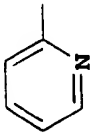
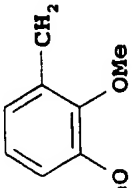
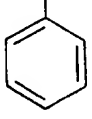
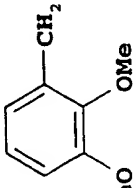
Compound DU	$CH_3-(CH_2)_2-$		C34H42N4O8	7.4, 100%	652 $[M+18]^+$	
Compound DV			C37H47N5O8	5.6, 50%	690	
Compound DW			C38H43N5O8	2.3, 84%	698	
Compound DX			C37H44N6O8	2.1, 100%	701	
Compound DY	$HO-(O=)C-(CH_2)_3-$		C32H40N6O8	2.3, 41%,	637	
Compound DZ			C35H45N7O7	2.4, 55%,	676	
Compound EA	$CH_3C(=O)-NH-(CH_2)_2-$		C32H41N7O7	2.2, 55%	636	

Compound EB			C34H39N7O6	2.2, 34%,	642	
Compound EC	$CH_3-(CH_2)_2-$		C31H40N6O6	1.7, 100%	593	
Compound ED			C34H45N7O6	6.0, 26%,	648	
Compound EE			C35H41N7O6	2.1, 72%	656	
Compound EF			C34H42N8O6	2.1, 66%	659	
Compound EG	$HO-(O=)C-(CH_2)_3-$		C35H42N4O8	7.3, 66%, 8.5, 34%	598	
Compound EH			C38H47N5O7	7.4, 65%	703 $[M+18]^+$	
Compound EI	$CH_3C(=O)-NH-(CH_2)_2-$		C35H43N5O7	7.0, 71%	646	
Compound EJ			C37H41N5O6	7.5, 50%, 7.8, 24%, 8.6, 27%	652	

Compound EK			C34H42N4O6	8.9, 72%	620 $[M+18]^+$	
Compound EL			C37H47N5O6	7.5, 56% 8.6, 38%	658	
Compound EM			C38H43N5O6	7.3, 65%, 8.6, 35%	666	
Compound EN			C37H44N6O6	6.8, 64%, 8.6, 36%	669	
Compound EO			C38H42N4O8	14.1, 89%	683	681
Compound EP			C38H48N4O8	15.3, 92%	689	687
Compound EQ			C39H44N4O8	14.5, 84%	697	
Compound ER			C40H46N4O8	15.0, 83%	711	709

Compound ES			C36H43N5O7	13.4,87%	658	656
Compound ET			C36H49N5O7	14.5, 88%	664	662
Compound EU			C37H45N5O7	13.9, 89%	672	670
Compound EV			C38H47N5O7	14.4, 84%	686	684
Compound EW			C35H40N6O6	12.8, 81%	641	639
Compound EX			C35H46N6O6	13.9, 30%	647	645
Compound EY			C36H42N6O6	13.2, 51%	655	653
Compound EZ			C37H44N6O6	13.7, 45%	669	667

Compound FA			C38H42N4O6	16.8, 92%		
Compound FB			C38H48N4O6	18.1, 92%	657	655
Compound FC			C39H44N4O6	17.2, 92%	665	663
Compound FD			C40H46N4O6	17.7, 86%	679	677
Compound FE			C38H47N5O9	13.4, 73%	718	716
Compound FF			C38H42N4O8	15.9, 82%	683	681
Compound FG			C38H48N4O8	17.1, 83%	689	687
Compound FH			C39H44N4O8	16.5, 82%	697	695

Compound FI			C38H43N5O8	13.0, 85%	698	696
Compound FJ			C40H46N4O8	16.8, 70%	711	709

EXAMPLE 4

Compounds FK to KV

Step 1. Resin A from Step 1 Example 2 was suspended in dimethylformamide (30ml) and then treated with phenethylamine (10 eqivalents). After standing at room temperature overnight the mixture was filtered to give resin G which was washed with (i) dimethylformamide, (ii) tetrahydrofuran, (iii) dichloromethane and then dried in a desiccator under high vacuum for 2 hours.

By proceeding in a similar manner but replacing phenethylamine by allylamine, isobutylamine, (cyclohexyl)methylamine, 3-(2-oxo-1-pyrrolydinyl)prop-1-ylamine, 4-phenyl-1-butylamine, piperonylamine, 3-(1-imidazolyl)prop-1-ylamine, 3-(2-methyl-1-piperdinyl)prop-1-ylamine, 2-(2-pyridinyl)ethylamine, (2-acetamido)ethylamine or 2-methoxybenzylamine there were prepared resins H to R.

A library of 144 compounds were prepared from resins H to R, using an ACT496 robot (96 well plate format), in the following manner.

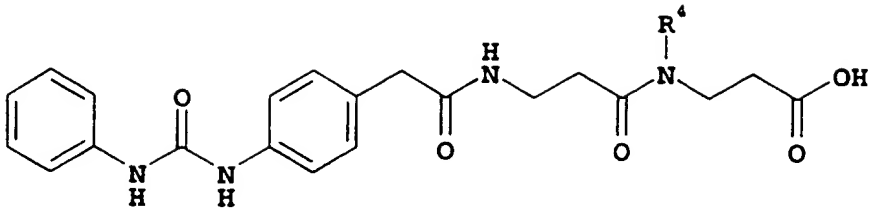
Step 2. The appropriate resin (40mg, resins H to S prepared as described above) was placed in each well and treated with dimethylformamide (1.2ml) for 5 minutes and then drained. Dimethylformamide (0.35 ml) was added to each well, the system was warmed to 30°C, and each well was treated with (i) a solution of diisopropylethylamine in dimethylformamide (0.5ml, 0.66M), (ii) a solution of N-(9-fluorenylmethoxycarbonyl)glycine in dimethylformamide (0.375ml, 0.294M) and (iii) a solution of [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] in dimethylformamide (0.375ml, 0.294M). After standing at 30°C for 2 hours with mixing the wells were drained and the resins in each well were then washed five times with dimethylformamide (1.2ml) with mixing for 5 minutes. Further batches of resins H to S were similarly modified by replacing N-(9-fluorenylmethoxycarbonyl)glycine with N-(9-fluorenylmethoxycarbonyl)-3-aminopropionic acid, N-(9-fluorenylmethoxycarbonyl)-4-aminobutyric acid, N-(9-fluorenylmethoxycarbonyl)sarcosine or N-(9-fluorenylmethoxycarbonyl)-4-N-methylaminobutyric acid.

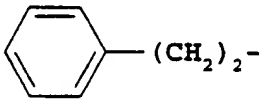
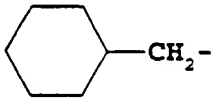
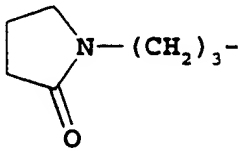
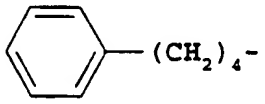
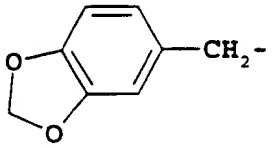
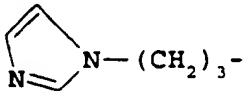
Step 3. The resins from Step 2 in each well were then treated with 20% piperidine in dimethylformamide (1.2ml) with mixing for 5 minutes, the wells were drained and the procedure repeated. The resins in each well were then washed (with mixing for 5 minutes) seven times with dimethylformamide (1.2ml).

Step 4. Dimethylformamide (0.35 ml) was added to th esin in each well followed by (i) a solution of diisopropylethylamine in dimethylformamide (0.5ml, 0.44M), (ii) a solution of 4-(phenylureido)phenylacteic acid in dimethylformamide (0.375ml, 0.196M), (iii) a solution of [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] in dimethylformamide (0.375ml, 0.196M). After mixing for 2 hours the wells drained and each well was washed (with mixing for 5 minutes) (i) three times with dimethylformamide (1.2ml), (ii) five times with tetrahydrofuran (1.2ml), (iii) seven times with dichloromethane (1.2ml). Further batches of resins from Step 3 were similarly modified by replacing [4-(phenylureido)phenyl]-acetic acid with [4-(3-o-tolylureido)phenyl]-acetic acid, [4-(phenylureido)phenyl]-propionic acid, [3-(phenylureido)phenyl]-acetic acid, [3-methoxy-4-(3-o-tolyl-ureido)phenyl]-acetic acid or [3-methoxy-4-(3-o-tolyl-ureido)phenyl]-propionic acid.

Step 5. The system heating was switched off. The resins in each well were treated with a mixture of trifluoroacetic acid and dichloromethane (2ml, 1:1 v/v) for 45 minutes, the filtrate was collected and the procedure repeated once more. The combined filtrates were evaporated on a turbovap evaporator (vortexed N_2 gas) to give Compounds FK to KV depicted in tables 3 to 15. The retention times (R_T), and area of main peak as a percentage of the total sample, shown in tables 3 to 15 were determined under HPLC conditions using as elutant (i) mixture of 0.05% trifluoroacetic acid in acetonitrile and 0.05% trifluoroacetic acid in water (1:19, v/v) for 2 minutes (ii) a mixture of 0.05% trifluoroacetic acid in acetonitrile and 0.05% trifluoroacetic acid in water (1:19 to 19:1, v/v) gradient elution over 10 minutes, (iii) a mixture of 0.05% trifluoroacetic acid in acetonitrile and 0.05% trifluoroacetic acid in water (19:1, v/v) for 2 minutes, (iv) a mixture of 0.05% trifluoroacetic acid in acetonitrile and 0.05% trifluoroacetic acid in water (19:1 to 1:19, v/v) gradient elution over 2 minutes.

Table 3



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound FK		C29H32N4O5	14.0, >75%	517	
Compound FL	$CH_2=CH-CH_2-$	C24H28N4O5	12.0, >90%	453	
Compound FM	$(CH_3)_2CH-CH_2-$	C25H32N4O5	13.1, >90%	469	
Compound FN		C28H36N4O5	14.8, >90%	509	
Compound FO		C28H35N5O6	11.0, >90%	560 $[M+Na]^+$	
Compound FP		C31H36N4O5	15.2, >90%		
Compound FQ		C29H30N4O7	13.6, >75%	569 $[M+Na]^+$	
Compound FR		C27H32N6O5	10.0, >75%	521	

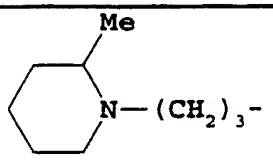
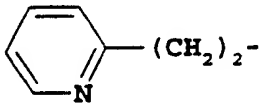
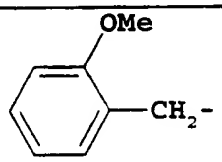
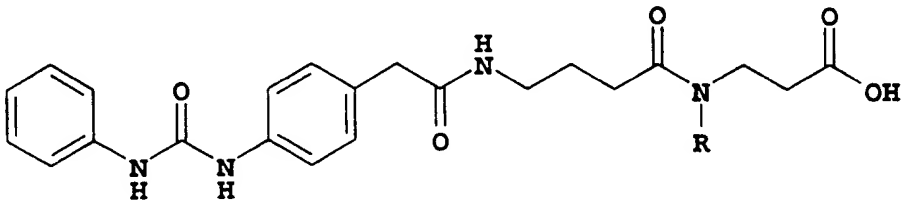
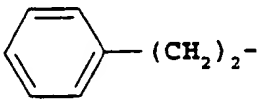
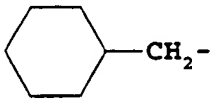
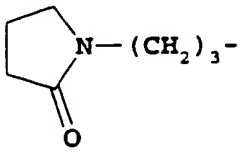
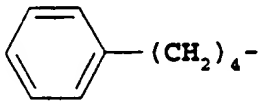
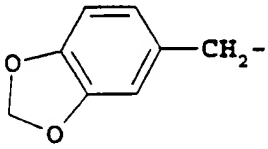
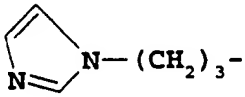
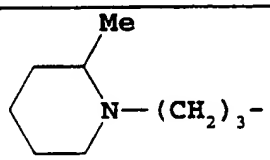
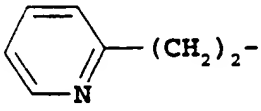
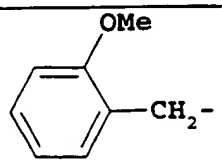
Compound FS		C30H41N5O5	11.3, >90%	552	
Compound FT		C28H31N5O5	10.2, >90%	518	
Compound FU		C25H31N5O6	10.1, >90%	498	
Compound FV		C29H32N4O6	13.7 ,>75%	533	

Table 4



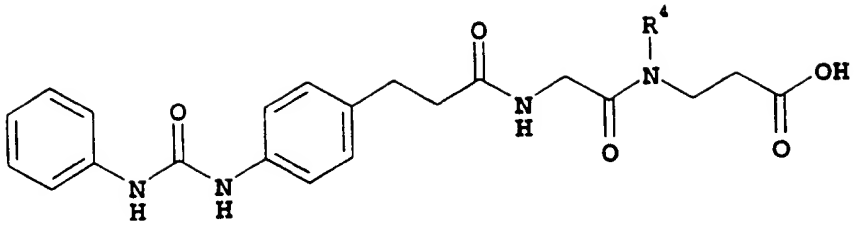
5

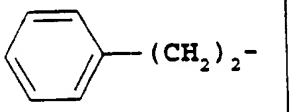
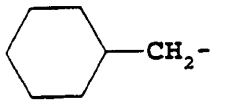
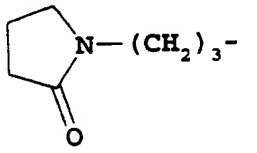
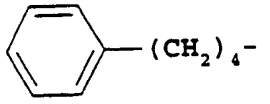
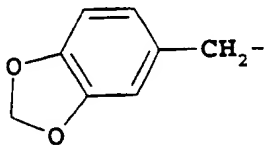
Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound FW		C30H34N4O5	10.3, >75%	531	
Compound FX	$CH_2=CH-CH_2-$	C25H30N4O5	13.9, >50%	467	
Compound FY	$(CH_3)_2CH-CH_2-$	C26H34N4O5	14.7, >50%	483	

Compound FZ		C29H38N4O5	11.0, <50%	537	
Compound GA		C29H37N5O6	13.7, >75%		550
Compound GB		C32H38N4O5	10.8, >75%	559	
Compound GC		C30H32N4O7	9.9, >75%		559
Compound GD		C28H34N6O5	8.4, >75%		533
Compound GE		C31H43N5O5	8.8, >75%		564
Compound GF		C29H33N5O5	8.5, >75%		530
Compound GG	$CH_3C(=O)NH-(CH_2)_2-$	C26H33N5O6	8.5, >75%		510
Compound GH		C30H34N4O6	10.0, >75%		545

5

Table 5



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound GI		C29H32N4O5	14.0, >75%	517	
Compound GJ	$CH_2=CH-CH_2-$	C24H28N4O5	12.0, >90%	453	
Compound GK	$(CH_3)_2CH-CH_2-$	C25H32N4O5	13.1, >90%	469	
Compound GL		C28H36N4O5	14.8, >90%	509	
Compound GM		C28H35N5O6	11.0, >90%	560 $[M+Na]^+$	
Compound GN		C31H36N4O5	15.2, >90%		
Compound GO		C29H30N4O7	13.6, >75%	569 $[M+Na]^+$	

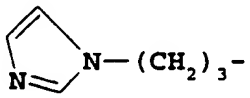
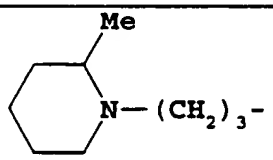
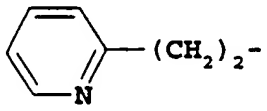
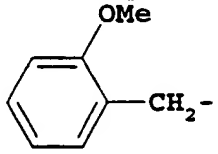
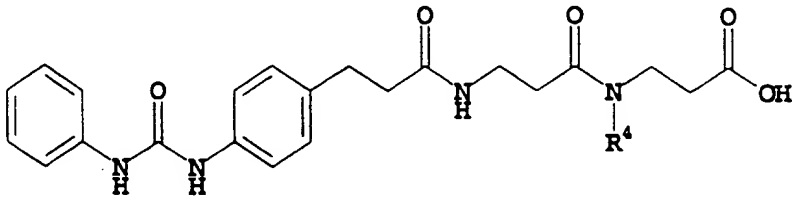
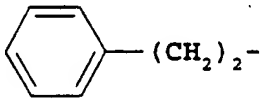
Compound GP		C27H32N6O5	10.0, >75%	521	
Compound GQ		C30H41N5O5	11.3, >90%	552	
Compound GR		C28H31N5O5	10.2, >90%	518	
Compound GS	$CH_3C(=O)NH-(CH_2)_2-$	C25H31N5O6	10.1, >90%	498	
Compound GT		C29H32N4O6	13.7, >75%	533	

Table 6



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound GU		C30H34N4O5	13.8, >90%	531	
Compound GV	$CH_2=CH-CH_2-$	C25H30N4O5	11.9, >90%	467	

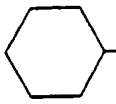
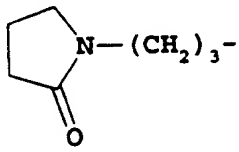
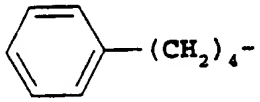
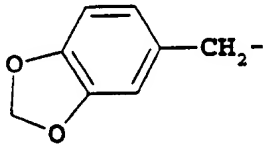
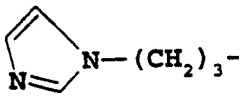
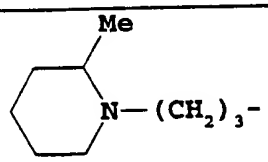
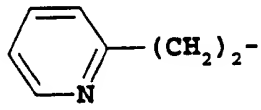
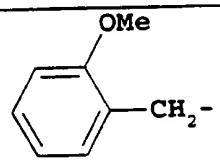
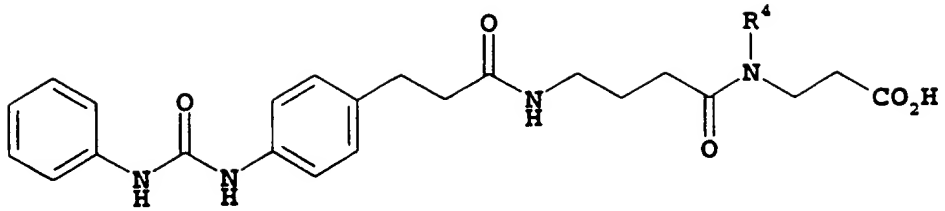
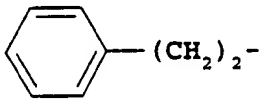
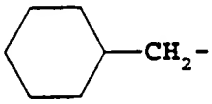
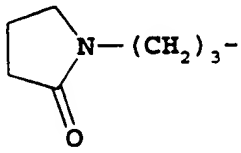
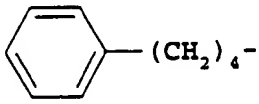
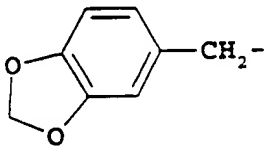
Compound GW	$(CH_3)_2CH-CH_2-$	C26H34N4O5	12.6, >90%	483	
Compound GX		C29H38N4O5	14.3, >90%	523	
Compound GY		C29H37N5O6	11.5, >90%	614 $[M+Na]^+$	
Compound GZ		C32H38N4O5	15.7, >95%	621 $[M+Na]^+$	
Compound HA		C30H32N4O7	14.0, >90%	623 $[M+Na]^+$	
Compound HB		C28H34N6O5	10.6, >90%	575	
Compound HC		C31H43N5O5	8.9, >75%		564
Compound HD		C29H33N5O5	8.4, >75%		530
Compound HE	$CH_3C(=O)NH-(CH_2)_2-$	C26H33N5O6	8.5, >90%		510
Compound HF		C30H34N4O6	10.1, >90%		545

Table 7



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound HG		C31H36N4O5	10.7, >90%	545	
Compound HH	$CH_2=CH-CH_2-$	C26H32N4O5	14.1, >75%	481	
Compound HI	$(CH_3)_2CH-CH_2-$	C27H36N4O5	9.9, >75%	497	
Compound HJ		C30H40N4O5	11.1, >75%	537	
Compound HK		C30H39N5O6	8.8, >75%		564
Compound HL		C33H40N4O5	10.8, >90%		571
Compound HM		C31H34N4O7	10.0, >90%		573

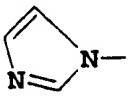
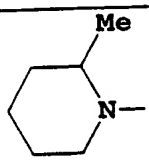
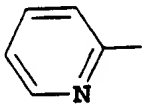
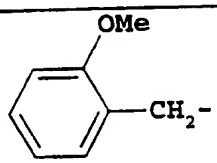
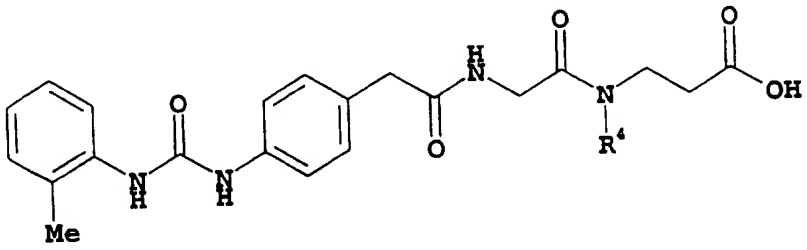
Compound HN		C29H36N6O5	8.5, >75%		547
Compound HO		C32H45N5O5	8.9, >90%		578
Compound HP		C30H35N5O5	8.5, >90%		544
Compound HQ	$CH_3C(=O)NH-(CH_2)_2-$	C27H35N5O6	8.6, >90%		524
Compound HR		C31H36N4O6	8.2, >95%		559

Table 8



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound HS		C29H32N4O5	14.2, >75%	517	
Compound HT	$CH_2=CH-CH_2-$	C24H28N4O5	12.0, >90%	453	

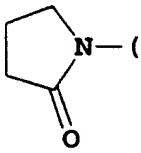
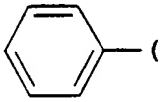
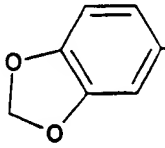
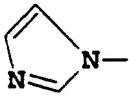
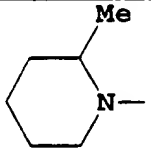
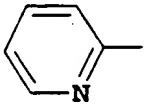
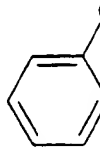
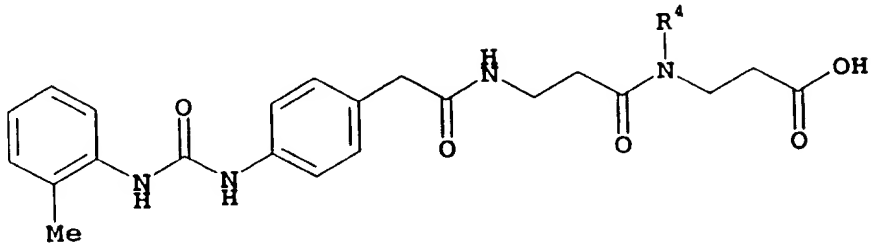
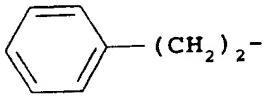
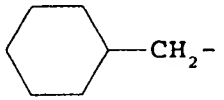
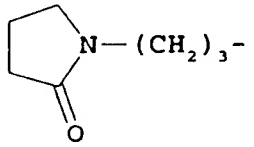
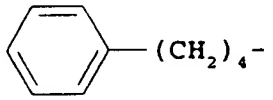
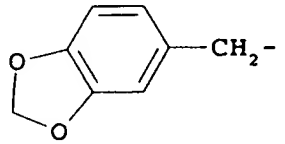
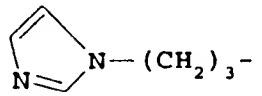
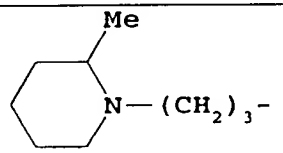
Compound HU	$(CH_3)_2CH-CH_2-$	C25H32N4O5	13.1, >90%	469	
Compound HV		C28H36N4O5	14.9, >90%	509	
Compound HW		C28H35N5O6	11.0, >90%	560 $[M+Na]^+$	
Compound HX		C31H36N4O5	15.4, >90%	567 $[M+Na]^+$	
Compound HY		C29H30N4O7	13.7, >75%	569 $[M+Na]^+$	
Compound HZ		C27H32N6O5	10.0, >75%	521	
Compound JA		C30H41N5O5	11.2, >90%	552	
Compound JB		C28H31N5O5	10.2, >90%	518	
Compound JC	$CH_3C(=O)NH-(CH_2)_2-$	C25H31N5O6	10.0, >90%	498	
Compound JD		C29H32N4O6	13.7, >75%	533	

Table 9



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound JF		C30H34N4O5	13.8, >90%	531	
Compound JG	$CH_2=CH-CH_2-$	C25H30N4O5	11.9, >90%	467	
Compound JH	$(CH_3)_2CH-CH_2-$	C26H34N4O5	12.8, >90%	483	

Compound JI		C29H38N4O5	14.5, >90%	523	
Compound JJ		C28H37N5O6	11.5, >90%	614 $[M+Na+CH_3CN]^+$	
Compound JK		C32H38N4O5	15.8, >95%		
Compound JL		C30H32N4O7	14.0, >90%	623 $[M+Na+CH_3CN]^+$	
Compound JM		C28H34N6O5	10.3, >90%	575 $[M+CH_3CN]^+$	
Compound JN		C31H43N5O5	8.9, >50%		564

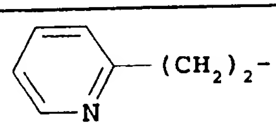
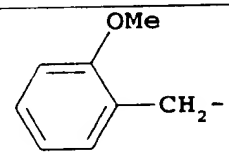
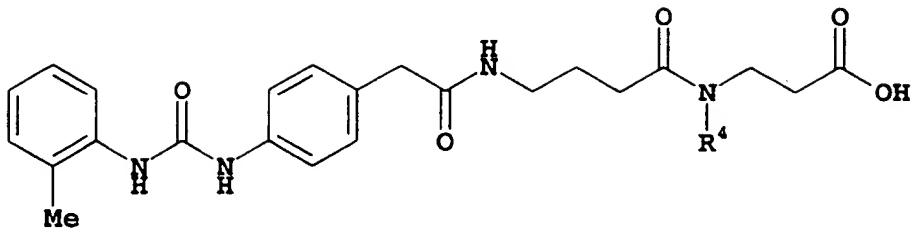
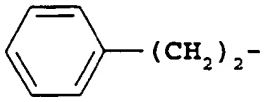
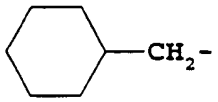
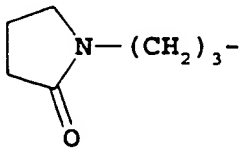
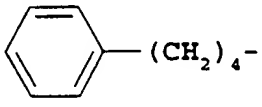
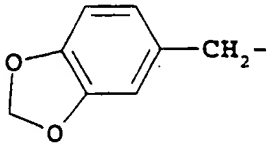
Compound JO		C29H33N5O5	8.6, >50%		530
Compound JP	$CH_3C(=O)NH-(CH_2)_2-$	C26H33N5O6	8.6, >75%		510
Compound JQ		C30H34N4O6	10.1, >90%		545

Table 10



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound JR		C31H36N4O5	10.7, >75%	545	
Compound JS	$CH_2=CH-CH_2-$	C26H32N4O5	14.0, >75%	481	
Compound JT	$(CH_3)_2CH-CH_2-$	C27H36N4O5	10.0, >50%	497	
Compound JU		C30H40N4O5	11.1, >75%	537	
Compound JV		C30H39N5O6	8.9, >75%		564
Compound JW		C33H40N4O5	10.9, >90%		571
Compound JX		C31H34N4O7	10.0, >75%		573

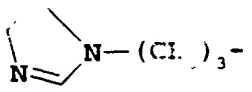
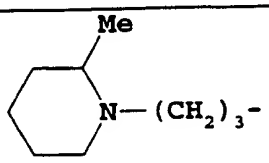
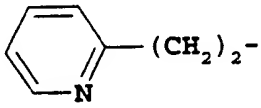
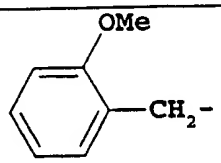
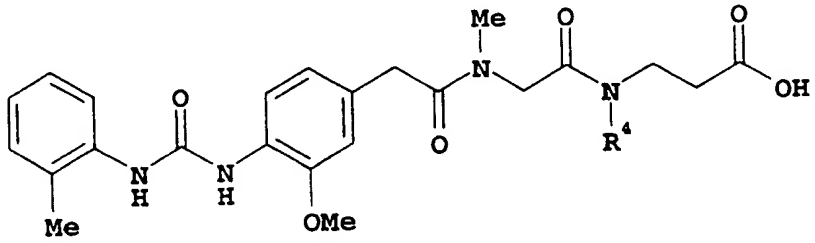
Compound JY		C29H36N6O5	8.6, >75%		547
Compound JZ		C32H45N5O5	9.0, >75%		578
Compound KA		C30H35N5O5	8.6, >75%		544
Compound KB	$CH_3C(=O)NH-(CH_2)_2-$	C27H35N5O6	8.7, >75%		524
Compound KC		C31H36N4O6	10.1, >95%		559

Table 11



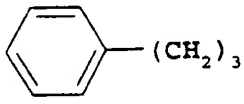
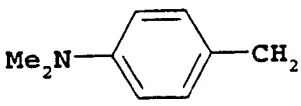
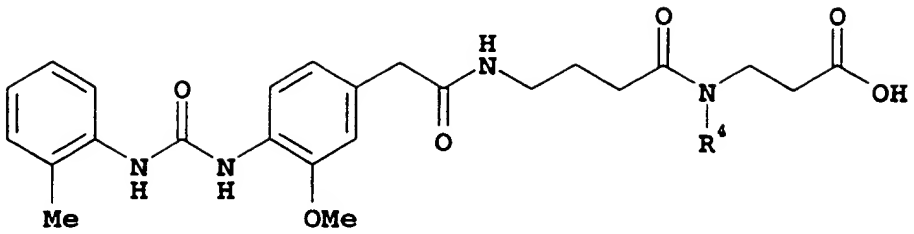
Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound KD		C32H38N4O6	8.0, 100%	575	573
Compound KF		C32H39N5O6	2.8, 100%		588

Table 12



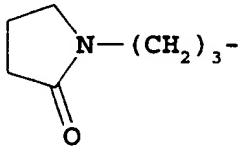
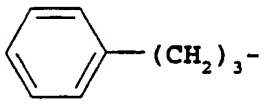
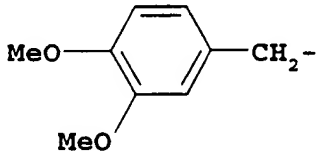
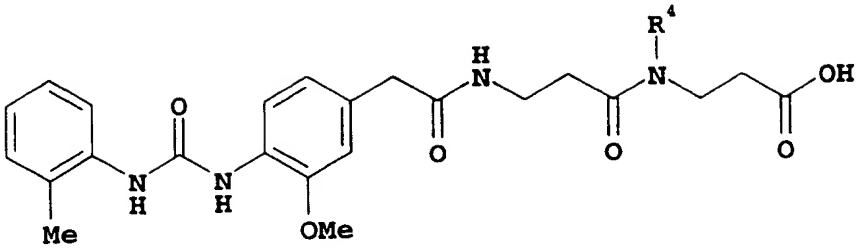
Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound KG		C31H41N5O7	2.7, 95%	596	594
Compound KH		C33H40N4O6	7.6, 97%		588
Compound KI		C33H40N4O8	5.8, 83%		620
Compound KJ		C33H41N5O6	2.5, 97%		602

Table 13



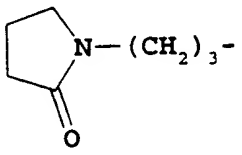
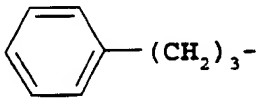
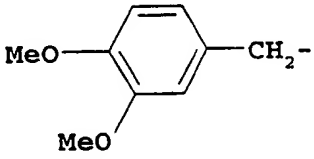
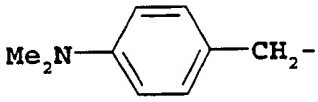
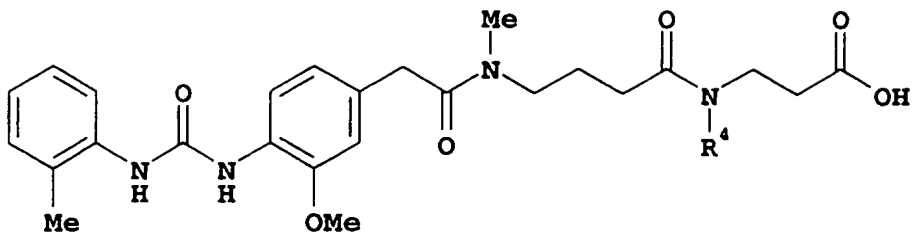
Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound KK		C30H39N5O7	2.7, 96%	582	580
Compound KL		C32H38N4O6	7.5, 97%	575	573
Compound KM		C32H38N4O8	5.9, 70%	607	
Compound KN		C32H39N5O6	2.4, 93%	590	

Table 14



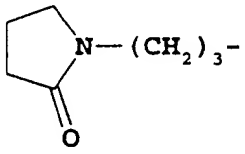
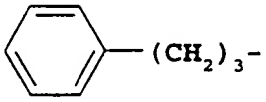
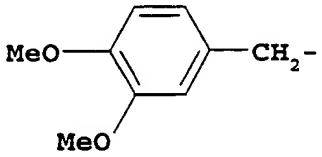
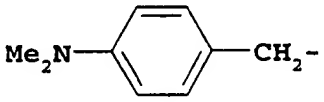
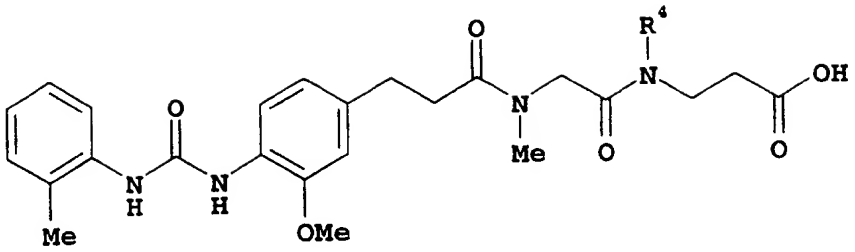
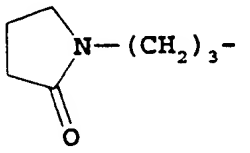
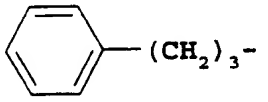
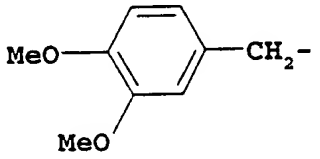
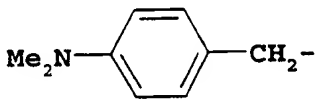
Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound KO		C32H43N5O7	3.0, 100%	610	609
Compound KP		C34H42N4O6	8.0, 85%	603	
Compound KQ		C34H42N4O8	6.3, 65%	635	
Compound KR		C34H43N5O6	2.6, 90%	618	

Table 15



Compound number	R^4	MOLECULAR FORMULA	HPLC R_T	MH^+	MH^-
Compound KS		C31H41N5O7	3.7, 96%		595
Compound KT		C33H40N4O6	8.4, 100%	590	587
Compound KU		C33H40N4O8	6.8, 100%	621	
Compound KV		C33H41N5O6	3.0, 88%		603

EXAMPLE 5

Compounds C, KW and KX

A solution of 3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid ethyl ester [2.0g, Reference Example 4(a)] in ethanol (50ml) was treated with sodium hydroxide (3.5ml, 1M). After stirring at room temperature for 3 hours the mixture was concentrated to dryness. The residue was dissolved in water (12ml) and the pH of the solution was adjusted to1.0 by addition of concentrated hydrochloric acid (0.25ml) and then extracted three times with dichloromethane. The resultant solid was collected and recrystallised twice from 20% aqueous isopropanol to give

3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid (Compound C) as a white solid (0.25g,), m.p. 183-187°C. [Elemental analysis:- C,63.2; H,6.3; N,9.2% Calculated for $C_{32}H_{38}N_4O_8$:- C,63.4; H,6.3; N,9.2%].

MS: 605 $[MH]^-$. HPLC: R_T=11.92 minutes (gradient elution using a mixture of acetonitrile and water 1:4 to 4:1).

(b) By proceeding in a manner similar to Example 5(a) but using 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid ethyl ester [Reference Example 4(b)] there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid (Compound KW) as a white foam. [Elemental analysis:- C,57.2; H,6.5; N,9.9%. Calculated for $C_{27}H_{34}N_4O_8 \cdot H_2O$:- C,57.2; H,6.3; N,9.8%]. MS: 543 $[MH]^+$.

(c) By proceeding in a manner similar to Example 5(a) but 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amino}-propionic acid ethyl ester [Reference Example 4(c)] there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amino}-propionic acid (Compound KX) as a yellow foam. [Elemental analysis:- C,59.5; H,6.5; N,11.9%. Calculated for $C_{29}H_{37}N_5O_7 \cdot H_2O$:- C,59.5; H,6.7; N,11.95%]. MS: 568 $[MH]^+$.

EXAMPLE 6

Compounds BD, D, LA, LB, LC, AO, AC and LD to LH

(a) Step 1. A solution of ({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetic acid [50g, Reference Example 3] and 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester [36g, Reference Example 2(a)] in dimethylformamide (500ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] (53.2g) and diisopropylethylamine (59ml). After stirring at ambient temperature for 3 hours the reaction mixture was evaporated to dryness and the residue was treated with water (3L). The mixture was extracted twice with ethyl acetate (1L) and then concentrated to dryness. The residue was subjected to flash chromatography on silica eluting initially with ethyl acetate and then with a mixture of ethyl acetate and methanol (9:1, v/v) to give 3-[N-(3,4-dimethoxybenzyl)-2-{2-[3-methoxy-4-(3-o-tolylureido)phenyl]acetylamino}acetamido]propionic acid ethyl ester as a yellow oil (49g).

Step 2. This material was treated with methanol (1L) and sodium hydroxide (160ml, 1.0M) and the reaction mixture was heated at 40°C for 2 hours. After this time, the reaction mixture was cooled then evaporated and then treated with water (1.5L). The aqueous solution was washed twice with ethyl acetate (500ml) and then acidified to pH 1.0 by addition of concentrated hydrochloric acid. The resultant solid was collected, washed with water and dried under vacuum. This material was recrystallised from 10% aqueous methanol to give 3-[N-(3,4-dimethoxy-benzyl)-2-{2-[3-methoxy-4-(3-o-tolylureido)phenyl]acetylamino}-acetamido]propionic acid (Compound BD) as a white solid (33g), m.p. 172-174°C. [Elemental analysis:- C,62.4; H,6.2; N,9.5%. Calculated for $C_{31}H_{36}N_4O_8$:- C,62.8; H,6.1; N,9.45%].

MS: 593 $[MH]^+$.

(b) By proceeding in a manner similar to Example 6(a) but using 3-(3-imidazol-1-yl-prop-1-ylamino)-propionic acid ethyl ester [Reference Example 2(b)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3{(3-imidazol-1-yl-prop-1-yl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid (Compound BK) as a white foam. MS: 551 $[MH]^+$.

(c) By proceeding in a manner similar to Example 6(a) but using 3-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-ylamino]-propionic acid ethyl ester [Reference Example 2(c)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid (Compound D) as a white foam. [Elemental analysis:- C,58.9; H,6.2; N,11.5%. Calculated for $C_{29}H_{37}N_5O_7 \cdot H_2O$:- C,59.5; H,6.7; N,11.95%]. MS: 586 $[MH]^+$.

(d) By proceeding in a manner similar to Example 6(a) but using 3-(3-carboxy-prop-1-ylamino)-propionic acid di-ethyl ester [Reference Example 2(d)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid (Compound LA) as a white solid, m.p. 179-181°C. [Elemental analysis:- C,59.0; H,6.1; N,10.55%. Calculated for $C_{26}H_{32}N_4O_8$:- C,59.1; H,6.1; N,10.6%]. MS: 529 $[MH]^+$.

(e) By proceeding in a manner similar to Example 6(a) but using 3-[2-(2-oxo-pyrrolidin-1-yl)-ethylamino]-propionic acid ethyl ester [Reference Example 2(e)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-

tolylureido)phenyl]-acetyl}-amino)-acetyl]-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amino}-propionic acid (Compound LB) as a white foam. [Elemental analysis:- C,58.2; H,6.5; N,12.0% Calculated for $C_{28}H_{35}N_5O_7 \bullet H_2O$:- C,58.8; H,6.5; N,12.25%]. MS: 553 $[MH]^+$.

(f) By proceeding in a manner similar to Example 6(a) but using 3-(2-carboxy-ethylamino)-propionic acid di-ethyl ester [Reference Example 2(f)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(2-carboxy-ethyl)-amino}-propionic acid (Compound LC) as a white solid, m.p. 117-121°C. [Elemental analysis:- C,56.5; H,5.85; N,10.6% Calculated for $C_{25}H_{30}N_4O_8 \bullet H_2O$:- C,56.4; H,6.1; N,10.5%]. MS: 533 $[MH]^+$.

(g) By proceeding in a manner similar to Example 6(a) but using 3-(2,3-dimethoxy-benzylamino)-propionic acid ethyl ester [Reference Example 2(g)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{(2,3-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid (Compound AO) as a white solid, m.p. 134-136°C. [Elemental analysis:- C,63.0; H,6.6; N,9.6% Calculated for $C_{31}H_{36}N_4O_8$:- C,62.8; H,6.1; N,9.45%]. MS: 593 $[MH]^+$.

(h) By proceeding in a manner similar to Example 6(a) but using 3-(3-phenyl-prop-1-ylamino)-propionic acid ethyl ester [Reference Example 2(h)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-phenyl-prop-1-yl)-amino}-propionic acid (Compound AC) as a white solid, m.p. 149-150°C. [Elemental analysis:- C,65.65; H,6.1; N,9.7% Calculated for $C_{31}H_{36}N_4O_6$:- C,66.4; H,6.5; N,10.0%]. MS: 561 $[MH]^+$.

(i) By proceeding in a manner similar to Example 6(a) but using 3-(phenylamino)-propionic acid ethyl ester (prepared according to the procedure described by Kano, Shinzo; Ebata, Tsutomu; Shibuya, Shiroshi. J. Chem. Soc., Perkin Trans. 1 (1980), Issue 10, 2105-11) to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-phenyl-amino}-propionic acid (Compound LD) as a beige solid. MS: 519 $[MH]^+$.

(k) By proceeding in a manner similar to Example 6(a) but using 3-(3-ethoxy-4-methoxy-benzylamino)-propionic acid ethyl ester [Reference Example 7(a)] to replace 3-(3,4-dimethoxy-

benzylamino)-propionic acid ethyl ester, there was prepared 3-{(3-ethoxy-4-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid (Compound LE) as a white solid, m.p. 187-189°C. [Elemental analysis:- C,63.1; H,6.5; N,9.2% Calculated for $C_{32}H_{38}N_4O_8$:- C,63.35; H,6.3; N,9.2%]. MS: 607 $[MH]^+$.

(l) By proceeding in a manner similar to Example 6(a) but using 3-(3,4-diethoxy-benzylamino)-propionic acid ethyl ester [Reference Example 7(b)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{(3,4-diethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid (Compound LF) as a white solid, m.p. 197-198°C. [Elemental analysis:- C,63.95; H,6.4; N,8.9% Calculated for $C_{33}H_{40}N_4O_8$:- C,63.9; H,6.5; N,9.0%]. MS: 621 $[MH]^+$.

(m) By proceeding in a manner similar to Example 6(a) but using 3-(4-benzyloxy-3-methoxy-benzylamino)-propionic acid ethyl ester [Reference Example 7(c)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{(4-benzyloxy-3-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid (Compound LG) as a white solid, m.p. 160-162°C. [Elemental analysis:- C,65.7; H,5.9; N,8.35% Calculated for $C_{37}H_{40}N_4O_8 \cdot 0.26H_2O$:- C,66.0; H,6.1; N,8.3%]. MS: 669 $[MH]^+$.

(n) By proceeding in a manner similar to Example 6(a) but using 3-[(1,4-benzodioxan-6-yl)-methylamino]-propionic acid ethyl ester [Reference Example 7(d)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[(1,4-benzodioxan-6-yl)-methyl]-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid (Compound LH) as a white solid, m.p. 175-178°C (with decomposition). [Elemental analysis:- C,62.0; H,6.1; N,9.5%. Calculated for $C_{31}H_{34}N_4O_8 \cdot 0.55H_2O$:- C,62.0; H,5.9; N,9.3%]. MS: 591 $[MH]^+$.

EXAMPLE 7

Compound LI

Step1. By proceeding in a manner similar to step 1 of Example 6(a) but using 3-(3-tert-butoxycarbonylamino-prop-1-ylamino)-propionic acid ethyl ester [Reference Example 2(i)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-tert-butoxycarbonylamino-prop-1-yl)-amino}-propionic acid ethyl ester.

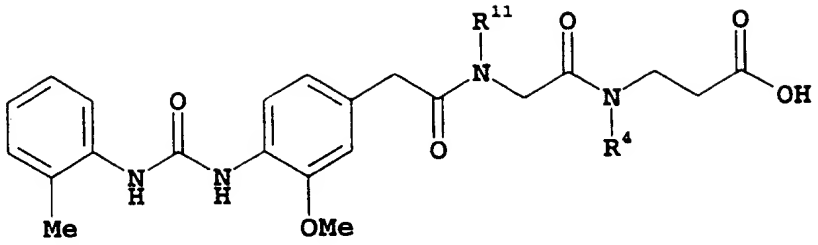
Step2. A solution of this material (0.75g) in dichloromethane (10ml) was treated with trifluoracetic acid (1.75ml) and stirred at ambient temperature for 2.5 hours. The reaction mixture was evaporated to give 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-amino-prop-1-yl)-amino}-propionic acid ethyl ester trifluoroacetate salt (1.0g) which was treated with dichloromethane (10ml). The resulting solution was cooled to 0°C and then treated with triethylamine (1.8ml) followed by methanesulphonyl chloride (0.1ml). The reaction mixture was stirred for 3 hours at ambient temperature then diluted with dichloromethane (10ml) and washed with hydrochloric acid (10ml, 1M), then with water (10ml), then with saturated sodium bicarbonate solution (10ml) and then with brine. The organic layer was dried over magnesium sulphate and evaporated. The residue was subjected to flash chromatography on silica eluting with a mixture of ethyl acetate and methanol (9:1, v/v) to give a white foam (0.63g). This material was hydrolysed according to the procedure described in step 2 of Example 3(a) to give 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-(3-methanesulphonylamino-prop-1-yl)-amino}-propionic acid (Compound LI) as a colourless foam (0.43g). MS: 578 $[MH]^+$.

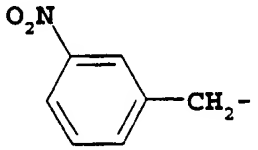
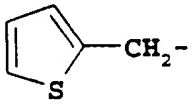
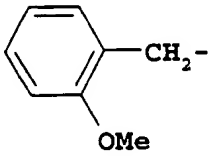
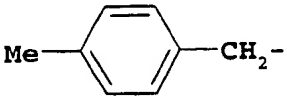
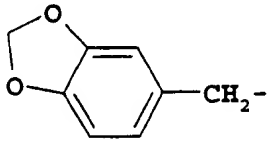
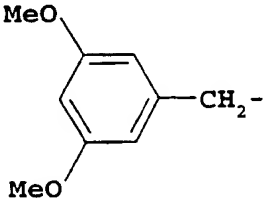
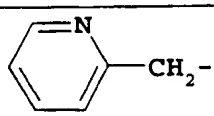
EXAMPLE 8

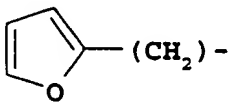
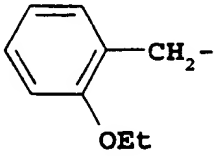
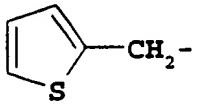
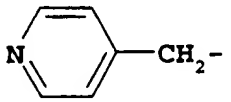
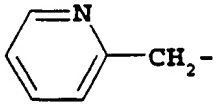
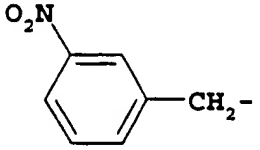
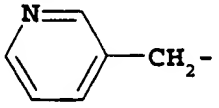
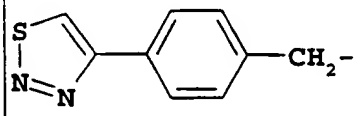
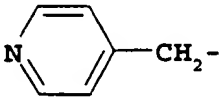
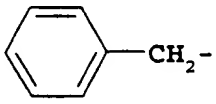
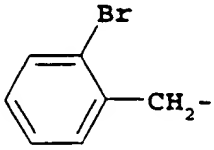
Compounds LJ to MD

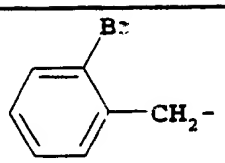
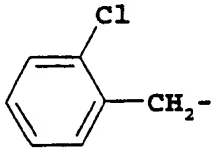
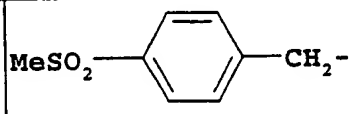
By proceeding in a similar manner to Example 3, but using the appropriately substituted amines in step 2 and ({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetic acid (Reference Example 1) or ({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetic acid (Reference Example 3) in step 3 there were prepared Compounds LJ to MD depicted in Table 16.

Table 16



Compound number	R^{11}	R^4	MOLECULAR FORMULA	MH^+	MH^-
Compound LJ	H		C29H31N5O8	578	576
Compound LK	CH_3		C28H32N4O6S		
Compound LL	CH_3		C31H36N4O7	577	575
Compound LM	CH_3		C31H36N4O6	561	559
Compound LN	CH_3		C31H34N4O8	591	589
Compound LO	CH_3		C32H38N4O8	607	605
Compound LP	H		C28H31N5O6	534	532

Compound LQ	CH_3		C28H32N4O7	537	535
Compound LR	CH_3		C32H38N4O7	591	589
Compound LS	H		C27H30N4O6S	539	537
Compound LT	H		C28H31N5O6	534	532
Compound LU	CH_3		C29H32N5O6	548	546
Compound LV	CH_3		C30H33N5O8	592	
Compound LW	CH_3		C29H33N5O6	548	546
Compound LX	CH_3		C32H34N6O6S	631	629
Compound LY	CH_3		C29H33N5O6	548	546
Compound LZ	CH_3		C30H34N4O6	547	545
Compound MA	CH_3		C30H33BrN4O6		624

Compound MB	H		C29H31BrN4O6	613	611
Compound MC	CH_3		C30H33ClN4O6	581	579
Compound MD	CH_3		C31H36N4O8S	625	623

EXAMPLE 9

(a) 3-{(3,4-Dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid sodium salt

A solution of 3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid [17g, Example 5(a)] in ethanol (170ml) was treated with sodium hydroxide solution (23.3ml, 1N). After stirring at ambient temperature for 24 hours the reaction mixture was filtered through a short pad of diatomaceous earth and then evaporated. The residue was triturated with hot ethyl acetate (200ml) and dried under vacuum. The resultant foam was dissolved in water (200ml) and freeze dried for 40 hours to yield the title compound as a white solid (15.4g), m.p. 225°C (with decomposition). [Elemental analysis:- C,57.8; H,6.05; N,8.2; Na,3.5%. Calculated for $C_{32}H_{37}N_4NaO_8 \cdot 2H_2O$:- C,57.8; H,6.2; N,8.4; Na,3.5%].

(b) By proceeding in a manner similar to Example 9(a) but using 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid [Example 1(a)], there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid sodium salt, m.p. 213°C (with decomposition). [Elemental analysis:- C,57.55; H,6.4; N,10.85; Na,3.5% Calculated for $C_{30}H_{38}N_5NaO_7 \cdot H_2O$:- C,57.95; H,6.5; N,11.25; Na,3.7%].

(c) By proceeding in a manner similar to Example 9(a) but using 3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid [Example 6(a)], there was prepared 3-{[({[3-methoxy-4-(3-o-tolyl-ureido)-phenyl]-acetyl}-amino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid sodium salt, m.p. >250°C (with decomposition).

REFERENCE EXAMPLE 1

({[3-Methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetic acid

A solution of [3-methoxy-4-(3-o-tolylureido)phenyl]-acetic acid (2.50g, Reference Example 5) and sarcosine ethyl ester hydrochloride(1.23g) in dimethylformamide (75ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] (3.03g) and diisopropylethylamine (4.30ml). The reaction mixture was stirred at room temperature for 2 hours, then treated with water (200ml) and then filtered. The white solid was suspended in tetrahydrofuran (100ml) and the mixture was then treated with lithium hydroxide hydrate (0.45g) in water (20ml). After stirring for 45 minutes the mixture was concentrated to remove the tetrahydrofuran. The remaining aqueous phase was washed with ethyl acetate then acidified by addition of hydrochloric acid (1M), then extracted three times with ethyl acetate. The combined organic extracts were washed with brine, then dried over magnesium sulphate and then evaporated to yield the title compound (2.24g) as a white solid, m. p. 125-130°C (with decomposition). HPLC: R_T=10.83 minutes (gradient elution using a mixture of acetonitrile and water 1:4 to 4:1 v/v). MS(-ve) $[M-1]^-$ 384.

REFERENCE EXAMPLE 2

(a) 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester

A mixture of 3,4-dimethoxy-benzylamine (100g) and ethyl acrylate (65ml) in ethanol (2L) and cylcohexane (1L) was stirred at room temperature for 20 hours then evaporated to give the title compound as a colourless oil (154g). MS: 268 $[MH]^+$.

(b) By proceeding in a manner similar to Reference Example 2(a) but using 1-(3-aminoprop-1-yl)-imidazole there was prepared 3-(3-imidazol-1-yl-prop-1-ylamino)-propionic acid ethyl ester. MS: 226 $[MH]^+$.

(c) By proceeding in a manner similar to Reference Example 2(a) but using 1-(3-aminoprop-1-yl)-2-pyrrolidinone there was prepared 3-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-ylamino]-propionic acid ethyl ester. MS: 243 $[MH]^+$.

(d) By proceeding in a manner similar to Reference Example 2(a) but using 4-amino-butanoic acid ethyl ester there was prepared 3-(3-carboxy-prop-1-ylamino)-propionic acid di-ethyl ester.

(e) By proceeding in a manner similar to Reference Example 2(a) but using 1-(2-aminoethyl)-2-pyrrolidinone there was prepared, 3-[2-(2-oxo-pyrrolidin-1-yl)-ethylamino]-propionic acid ethyl ester.

(f) By proceeding in a manner similar to Reference Example 2(a) but using β-alanine ethyl ester there was prepared 3-(2-carboxy-ethylamino)-propionic acid di-ethyl ester.

(g) By proceeding in a manner similar to Reference Example 2(a) but using 2,3-dimethoxy-benzylamine, there was prepared 3-(2,3-dimethoxy-benzylamino)-propionic acid ethyl ester.

(h) By proceeding in a manner similar to Reference Example 2(a) but using 3-phenyl-prop-1-ylamine, there was prepared 3-(3-phenyl-prop-1-ylamino)-propionic acid ethyl ester.

(i) By proceeding in a manner similar to Reference Example 2(a) but using 3-(tert-butoxycarbonylamino)prop-1-ylamine (prepared according to the procedure described by Muller, Dan; Zeltser, Irena; Bitan, Gal; Gilon, Chaim. J. Org. Chem. 1997, 62, page 411-416), there was prepared 3-(3-tert-butoxycarbonylamino-prop-1-ylamino)-propionic acid ethyl ester.

REFERENCE EXAMPLE 3

({[3-Methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetic acid

A stirred solution of [3-methoxy-4-(3-o-tolylureido)phenyl]-acetic acid (7.53g, Reference Example 5) in a mixture of dimethylformamide (15ml) and dichloromethane (150ml) was treated with 1-(3-dimethylaminoprop-1-yl)-3-ethylcarbodiimide (4.98g), then with 1-hydroxybenzotriazole (3.57g), then with glycine methyl ester hydrochloride (3.01g) and then with diisopropylethylamine (4.10ml). After stirring at room temperature for 20 hours the reaction mixture was diluted with water (100ml). The organic phase was washed with saturated sodium bicarbonate (100ml), then with hydrochloric acid (1M) and then with brine, then dried over magnesium sulphate and then evaporated. The residue was triturated with petroleum ether and the resulting cream coloured solid (6.25g) was dissolved in tetrahydrofuran (200ml). The solution was treated with water (50ml) and then with lithium hydroxide hydrate (0.75g). The mixture was stirred at room temperature for 4 hours and then the tetrahydrofuran was removed

under vacuum. The aqueous phase was acidified by addition of hydrochloric acid (12M). The resulting solid was washed with diethyl ether and then dried to give the title compound (5.76g), m. p. 130-134°C (with decomposition). MS: 370 [M-1]$^-$. HPLC: R_T=10.16 minutes (gradient elution using a mixture of acetonitrile and water 4:1 to 1:4 v/v).

REFERENCE EXAMPLE 4

(a) 3-{(3,4-Dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid ethyl ester

A solution of ({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetic acid [18.4g, Reference Example 1] and 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester [13.4g, Reference Example 2(a)] in dimethylformamide (400ml) was treated with [O-(7-azabenzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexafluorophosphate] (19.1g) and diisopropylethylamine (10.5ml). After stirring at ambient temperature for 20 hours the reaction mixture was evaporated to dryness. The residue was treated with water (800ml) followed by hydrochloric acid (175ml, 1 M) and the mixture was extracted twice with ethyl acetate (500ml). The combined organic extracts were washed with hydrochloric acid (500ml, 1M), then with water (400ml), then with saturated aqueous sodium bicarbonate solution (500ml), then dried over magnesium sulphate and then evaporated. The residual oil was subjected to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (49:1, v/v) to give the title compound as a fawn coloured foam (26.4g), m.p. 97-105°C. [Elemental analysis:- C,63.4; H,6.7; N,8.7% Calculated for $C_{34}H_{42}N_4O_8 \cdot 0.5H_2O$:- C,63.3; H,6.8; N,8.8%].

(b) By proceeding in a manner similar to Reference Example 4(a) but using 3-(3-carboxy-prop-1-ylamino)-propionic acid di-ethyl ester [Reference Example 2(d)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid ethyl ester.

(c) By proceeding in a manner similar to Reference Example 4(a) but using 3-[2-(2-oxo-pyrrolidin-1-yl)-ethylamino]-propionic acid ethyl ester [Reference Example 2(e)] to replace 3-(3,4-dimethoxy-benzylamino)-propionic acid ethyl ester, there was prepared 3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[2-(2-oxo-pyrrolidin-1-yl)-ethyl]-amino}-propionic acid ethyl ester.

REFERENCE EXAMPLE 5

[3-Methoxy-4-(3-o-tolylureido)phenyl]acetic acid

A suspension of [3-methoxy-4-(3-o-tolylureido)phenyl]-acetic acid methyl ester (19.43g, Reference Example 6) in methanol (195ml) was treated with sodium hydroxide solution (65ml, 1N) and the mixture was heated at reflux for 1 hour giving a clear solution. The reaction mixture was cooled to room temperature and then filtered. The filtrate was diluted to 390ml with water, then heated to 50°C and then acidified to pH 1 by the addition of hydrochloric acid (80ml, 1N) over 1 hour. The resulting suspension was stirred for a further 30 minutes at 50°C, then allowed to cool to room temperature and then filtered. The solid was washed with twice with water (200ml) then dried to give the title compound (15.72g) as a white solid, m. p. 179-181°C (with decomposition).

REFERENCE EXAMPLE 6

[3-methoxy-4-(3-o-tolylureido)phenyl]-acetic acid methyl ester

A suspension of potassium t-butoxide (1.44kg) in dimethylformamide(6.6l), cooled to -5°C to -10°C, was treated with a mixture of 2-nitroanisole (690g) and methyl dichloroacetate (915g) over 4 hours, whilst maintaining the temperature below -5°C. The reaction mixture was then treated with acetic acid (770ml), then with water (6.6l) and then extracted three times with *tert*-butyl methyl ether (5.5l). The combined extracts were washed with water (5.5l), then with saturated sodium bicarbonate solution (5.5l), then with saturated brine (5.5l) and then dried over magnesium sulphate to give a solution of methyl α-chloro-3-methoxy-4-nitrophenylacetate. This solution was concentrated to half volume under reduced pressure and then treated with tetrahydrofuran (2l), followed by triethylamine (751ml), followed by 10% palladium on charcoal (58.4g) and the mixture was hydrogenated under a pressure of 50psi hydrogen at 50°C for 8 hours. The mixture was cooled to room temperature and filtered. The filtrate was dried over magnesium sulphate to give a solution of methyl 4-amino-3-methoxyphenylacetate which was heated to reflux and then treated with *o*-tolyl isocyanate (598.5g) over 30 minutes. After heating at reflux temperature for a further 3 hours, during which time a solid was deposited, the mixture was cooled to room temperature. The solid was collected, washed twice with *tert*-butyl methyl ether (4l), then dried in a vacuum oven at 60°C to give the title compound (764.8g) as a white solid, m.p. 167-168°C.

REFERENCE EXAMPLE 7

(a) 3-(3-Ethoxy-4-methoxy-benzylamino)-propionic acid ethyl ester

A mixture of β-alanine ethyl ester hydrochloride (1.6g), 3-ethoxy-4-methoxybenzaldehyde (1.8g), sodium cyanoborohydride (0.42g) and powdered 3Å molecular seives (2.5g) in ethanol (25ml) was stirred at ambient temperature for 24 hours. A further aliquot of sodium cyanoborohydride (0.42g) was added and stirring was continued for a further 24 hours. The reaction mixture was filtered and the filtrate was evaporated. The residue was treated with ethyl acetate (100ml) and the solution was washed with 10% aqueous potassium carbonate (50ml), then twice with water (25ml), then with brine (25ml), then dried over magnesium sulphate and then evaporated. The residual oil was subjected to flash chromatography on silica eluting with a mixture of dichloromethane and methanol (95:5, v/v) to give the title compound as a colourless oil (1.1g).

(b) By proceeding in a manner similar to Reference Example 7(a) but using 3,4-diethoxy-benzaldehyde, there was prepared 3-(3,4-diethoxy-benzylamino)-propionic acid ethyl ester.

(c) By proceeding in a manner similar to Reference Example 7(a) but using 4-benzyloxy-3-methoxy-benzaldehyde, there was prepared 3-(4-benzyloxy-3-methoxy-benzylamino)-propionic acid ethyl ester.

(d) By proceeding in a manner similar to Reference Example 7(a) but using 1,4-benzodioxan-6-carboxaldehyde, there was prepared 3-[(1,4-benzodioxan-6-yl)-methylamino]-propionic acid ethyl ester.

IN VITRO AND IN VIVO TEST PROCEDURES

1. Inhibitory effects of compounds on VLA4 dependent cell adhesion to Fibronectin and VCAM.

1.1 Metabolic labelling of RAMOS cells.

RAMOS cells (a pre-B cell line from ECACC, Porton Down, UK) are cultured in RPMI culture medium (Gibco, UK) supplemented with 5% foetal calf serum (FCS, Gibco, UK). Prior to assay the cells are suspended at a concentration of 0.5 X 10^6 cells/ml RPMI and labelled with 400μCi/100mls of [^{3}H]-methionine (Amersham, UK) for 18 hours at 37°C.

1.2 96 well plate preparation for adhesion assay.

Cytostar plates (Amersham, UK) were coated wi : 50µl/well of either 3µg/ml human soluble VCAM-1 (R&D Systems Ltd, UK) or 28.8µg/ml human tissue Fibronectin (Sigma, UK). In control non-specific binding wells 50µl phosphate buffered saline was added. The plates were then left to dry in an incubator at 25°C, overnight. The next day the plates were blocked with 200µl/well of Pucks buffer (Gibco, UK) supplemented with 1% BSA (Sigma, UK). The plates were left at room temperature in the dark for 2 hours. The blocking buffer was then disposed of and the plates dried by inverting the plate and gently tapping it on a paper tissue. 50µl/well of 3.6% dimethyl sulphoxide in Pucks buffer supplemented with 5mM manganese chloride (to activate the integrin receptor Sigma, UK) and 0.2% BSA (Sigma, UK), was added to the appropriate control test binding and non-specific binding assay wells in the plate. 50µl/well of the test compounds at the appropriate concentrations diluted in 3.6% dimethyl sulphoxide in Pucks buffer supplemented with 5mM manganese chloride and 0.2% BSA, was added to the test wells.

Metabolically labelled cells were suspended at 4 x 10^6 cells/ml in Pucks buffer that was supplemented with manganese chloride and BSA as above. 50µl/well of cells in 1.8% dimethyl sulphoxide in Pucks buffer and supplements was added to all plate wells.

The same procedure exists for plates coated with either VCAM-1 or fibronectin and data is determined for compound inhibition of cell binding to both substrates.

1.3 Performance of assay and data analysis.

The plates containing cells in control or compound test wells are incubated in the dark at room temperature for 1 hour.

The plates are then counted on a Wallac Microbeta scintillation counter (Wallac, UK) and the captured data processed in Microsoft Excel (Microsoft, US). The data was expressed as an IC50, namely the concentration of inhibitor at which 50% of control binding occurs. The percentage binding is determined from the equation:

$$\{[(C_{TB} - C_{NS})-(C_I - C_{NS})] / (C_{TB} - C_{NS})\}X\ 100 = \%\ \text{binding}$$

where C_{TB} are the counts bound to fibronectin (or VCAM-1) coated wells without inhibitor present, C_{NS} are the counts present in wells without substrate, and C_I are the counts present in wells containing a cell adhesion inhibitor.

Compound data of this invention is expressed for IC_{50}s for inhibition of cell adhesion to both fibronectin and VCAM-1.

Compound data of this invention is expressed as IC_{50}s for inhibition of cell adhesion to both fibronectin and VCAM-1. Particular compounds of the invention inhibit cell adhesion to fibronectin and VCAM-1 with IC50s in the range 100 micromolar to 0.01 nanomolar. Preferred compounds of the invention inhibit cell adhesion to fibronectin and VCAM-1 with IC50s in the range 1.0 micromolar to 0.01 nanomolar. Especially preferred compounds of the invention inhibit cell adhesion to fibronectin and VCAM-1 with IC50s in the range 100 nanomolar to 0.01 nanomolar.

2. Inhibition of antigen-induced airway inflammation in the mouse and rat.

2.1 Sensitization of the animals.

Rats (Brown Norway, Harland Olac, UK) are sensitized on days 0, 12 and 21 with ovalbumin (100 µg, intraperitoneally [i.p], Sigma, UK) administered with aluminium hydroxide adjuvant (100mg, i.p., Sigma, UK) in saline (1ml, i.p.).

In addition mice (C57) are sensitized on days 0 and 12 with ovalbumin (10µg, i.p.) administered with aluminium hydroxide adjuvant (20mg, i.p.) in saline (0.2ml, i.p.).

2.2 Antigen challenge.

Rats are challenged on any one day between days 28-38, while mice are challenged on any one day between days 20-30.

The animals are challenged by exposure for 30 minutes (rats) or 1 hour (mice) to an aerosol of ovalbumin (10g / l) generated by an ultrasonic nebulizer (deVilbiss Ultraneb, US) and passed into an exposure chamber.

2.3 Treatment protocols.

2.3 Treatment protocols.

Animals are treated as required before or after antigen challenge. The aqueous-soluble compounds of this invention can be prepared in water (for oral, p.o. dosing) or saline (for intratracheal, i.t. dosing). Non-soluble compounds are prepared as suspensions by grinding and sonicating the solid in 0.5 % methyl cellulose / 0.2 % polysorbate 80 in water (for p.o. dosing, both Merck UK Ltd., UK) or saline (for i.t. dosing). Dose volumes are: for rats 1ml / kg, p.o. or 0.5mg / kg, i.t.; for mice 10ml / kg, p.o. or 1ml / kg, i.t.

2.4 Assessment of airway inflammation.

The [illegible] accumulation in the lung is assessed 24 hours after challenge (rats) or 48-72 hours after challenge (mice). The animals are euthanized with sodium pentobarbitone (200mg/kg, i.p., Pasteur Merieux, France) and the trachea is immediately cannulated. Cells are recovered from the airway lumen by bronchoalveolar lavage (BAL) and from the lung tissue by enzymatic (collagenase, Sigma, UK) disaggregation as follows.

BAL is performed by flushing the airways with 2 aliquots (each 10 ml/kg) RPMI 1640 medium (Gibco, UK) containing 10 % fetal calf serum (FCS, Serotec Ltd., UK). The recovered BAL aliquots are pooled and cell counts made as described below.

Immediately after BAL, the lung vasculature is flushed with RPMI 1640 / FCS to remove the blood pool of cells. The lung lobes are removed and cut into 0.5 mm pieces. Samples (rats: 400mg; mice: 150mg) of homogenous lung tissue are incubated in RPMI 1640 / FCS with collagenase (20 U/ml for 2 hours, then 60 U/ml for 1 hour, 37°C) to disaggregate cells from the tissue. Recovered cells are washed in RPMI 1640 / FCS.

Counts of total leukocytes recovered from the airway lumen and the lung tissue are made with an automated cell counter (Cobas Argos, US). Differential counts of eosinophils, neutrophils and mononuclear cells are made by light microscopy of cytocentrifuge preparations stained with Wright-Giemza stain (Sigma, UK). T cells are counted by flow cytometry (EPICS XL, Coulter Electronics, US) using fluophore-labelled antibodies against CD2 (a pan-T cell marker used to quantify total T cells), CD4, CD8 and CD25 (a marker of activated T cells). All antibodies were supplied by Serotec Ltd., UK)

2.5 Data analysis.

The cell data was expressed as mean cell numbers in unchallenged, challenged and vehicle treated, and challenged and compound treated groups, including the standard error of the means. Statistical analysis of the difference among treatment groups was evaluated using one-way analysis of variance via the Mann-Whitney test. Where $p < 0.05$ no statistical significance existed. The inhibitors of the invention caused a statistically significant reduction in eosinophil and lymphocyte numbers in the BAL and airway tissue. The inhibitors of the invention caused a statistically significant reduction in eosinophil and lymphocyte numbers in the BAL and airway tissue at doses within the range 100 mg/kg to 0.01 mg/kg.

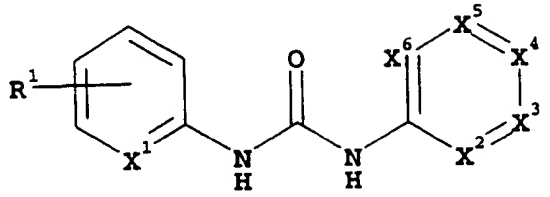
3. Inhibition of Antigen Induced Airway Sensitivity in Allergic Sheep

The experiment was performed essentially as described in W. M. Abraham et al, J. Clin. Invest., (1994) Vol 93, 776-787. The experiment used allergic sheep which had been previously shown to

develop early and late phase responses to inhaled challenge with Ascaris suum antigen. The inhibitors of the invention were delivered as an aerosol to the sheep and caused a statistically significant reduction of Ascaris suum induced airway responses when dosed at 1mg/kg.

CLAIMS

1. A compound of general formula (I):-



(I)

wherein:-

R^1 is hydrogen, halogen, lower alkyl or lower alkoxy;

X^1, X^2 and X^6 independently represent N or CR^2; and

one of X^3, X^4 and X^5 represents CR^3 and the others independently represents N or CR^2

[where R^2 is hydrogen, halogen, lower alkyl or lower alkoxy; and R^3 represents a group $-L^1-(CH_2)_n-C(=O)-N(R^4)-CH_2-CH_2-Y$ in which:

R^4 is aryl or heteroaryl, or R^4 is alkyl, alkenyl, alkynyl each optionally substituted by one or more groups chosen from halo, oxo, R^5, $-C(=O)-R^7$, $-NH-C(=O)-R^7$or $-C(=O)NY^1Y^2$, or R^4 is cycloalkenyl, cycloalkyl or heterocycloalkyl each optionally substituted by one or more groups chosen from oxo, R^6 or $-L^2-R^6$ {where R^5 is an acidic functional group (or corresponding protected derivative), aryl, cycloalkyl, cycloalkenyl, heteroaryl, heterocycloalkyl, $-ZR^7$ or $-NY^1Y^2$; R^6 is an acidic functional group (or corresponding protected derivative), aryl, heteroaryl, heterocycloalkyl, -ZH, $-Z^1R^7$ or $-NY^1Y^2$; R^7 is alkyl, aryl, arylalkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; L^2 is alkylene; Y^1 and Y^2 are independently hydrogen, acyl, alkyl [optionally substituted by hydroxy, heterocycloalkyl, or one or more carboxy or $-C(=O)-NHR^8$ groups (where R^8 is hydrogen or lower alkyl)], alkylsulphonyl, aryl, arylalkyloxycarbonyl, arylsulphonyl, arylalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl or heterocycloalkylalkyl; or the group $-NY^1Y^2$ may form a 5-7 membered cyclic amine which (i) may be optionally substituted with one or more substituents selected from carboxamido, carboxy, hydroxy, oxo, hydroxyalkyl, $HOCH_2CH_2-(OCH_2CH_2)_m-$ (where m is zero, or an integer one or two), or alkyl optionally substituted by carboxy or carboxamido (ii) may also contain a further heteroatom selected from O, N, S or SO_2 and (iii) may also be fused to additional aromatic, heteroaromatic,

heterocycloalkyl or cycloalkyl rings to form a bicyclic or tricyclic ring system; Z is O or S; and Z^1 is O or $S(O)_m$};

L^1 represents a $-R^9-R^{10}-$ linkage, in which R^9 is a straight or branched C_{1-6}alkylene chain, a straight or branched C_{2-6}alkenylene chain or a straight or branched C_{2-6}alkynylene chain, and R^{10} is a direct bond, cycloalkylene, heterocycloalkylene, arylene, heteroaryldiyl, $-C(=Z)-NR^{11}-$, $-NR^{11}-C(=Z)-$, $-Z^1-$, $-NR^{11}-$, $-C(=O)-$, $-C(=NOR^{11})-$, $-NR^{11}-C(=Z)-NR^{11}-$, $-SO_2-NR^{11}-$, $-NR^{11}-SO_2-$, $-O-C(=O)-$, $-C(=O)-O-$, $-NR^{11}-C(=O)-O-$ or $-O-C(=O)-NR^{11}-$ (where R^{11} is a hydrogen atom or R^4); but excluding compounds where an oxygen, nitrogen or sulphur atom is attached directly to a carbon carbon multiple bond;

Y is carboxy (or an acid bioisostere) or $-C(=O)-NY^1Y^2$; and

n is an integer from 1 to 6];

and their prodrugs, and pharmaceutically acceptable salts and solvates of such compounds and their prodrugs.

2. A compound according to claim 1 in which R^1 represents hydrogen.

3. A compound according to claim 1 or claim 2 in which X^1 represents CR^2 where R^2 is C_{1-4}alkyl or C_{1-4}alkoxy.

4. A compound according to claim 3 in which R^2 is methyl.

5. A compound according to any preceding claim in which X^2 represents CR^2 where R^2 is C_{1-4}alkyl or C_{1-4}alkoxy.

6. A compound according to claim 5 in which R^2 is methoxy.

7. A compound according to any preceding claim in which X^3 represents CH.

8. A compound according to any preceding claim in which X^6 represents CH.

9. A compound according to any preceding claim in which one of X^4 and X^5 represents CR^3 and the other represents CH.

10. A compound according to claim 9 in which within R^3 the moiety L^1 represents a $-R^9-R^{10}-$ linkage wherein R^9 represents a straight or branched C_{1-6}alkylene chain and R^{10} represents $-C(=O)-NR^{11}-$ where R^{11} is selected from one of the following groups :

(i) hydrogen;

(ii) C_{1-6}alkyl;

(iii) C_{1-6}alkyl substituted by R^5, where R^5 is aryl;

(iv) C_{1-6}alkyl substituted by R^5, where R^5 is heteroaryl;

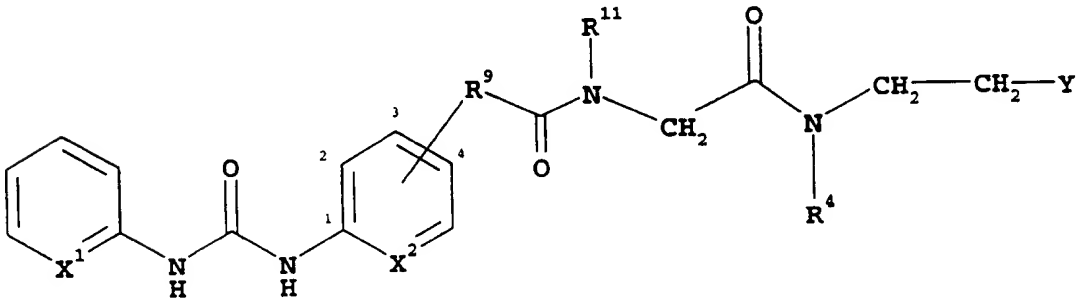
(v) C_{1-6}alkyl substituted by R^5, where R^5 is cycloalkyl;

(vi) C_{1-6}alkyl substituted by R^5, where R^5 is carboxy (or an acid bioisostere); or

(vii) C_{1-6}alkyl substituted by R^5, where R^5 is $-NY^1Y^2$.

11. A compound according to any preceding claim in which within R^3 the moiety n is 1.

12. A compound of formula (Ia):-



(Ia)

in which R^4, R^9, R^{11} and Y are as defined in claim 1, X^1 and X^2 each independently represent CR^2 (wherein each R^2 group is as defined in any one of claims 1, 3, 4, 5 or 6), and

$-R^9-CON(R^{11})-CH_2-CON(R^4)-CH_2-CH_2-Y$ is attached at the ring 3 or 4 position, and their prodrugs and pharmaceutically acceptable salts, and solvates (e.g. hydrates) of compounds of formula (Ia) and their prodrugs.

13. A compound according to any preceding claim in which R^9 represents straight or branched C_{1-4}alkylene.

14. A compound according to claim 13 in which R^9 represents methylene.

15. A compound according to any preceding claim in which R^{11} represents hydrogen, straight or branched C_{1-4}alkyl, straight or branched C_{1-3}alkyl substituted by aryl, heteroaryl, C_{3-8}cycloalkyl or carboxy, or straight or branched C_{2-3}alkyl substituted by $-NY^1Y^2$.

16. A compound according to any preceding claim in which R^4 represents straight or branched C_{1-10}alkyl.

17. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by R^5, where R^5 is aryl.

18. A compound according to claim 17 in which R^4 represents 3,4-diC_{1-3}alkoxybenzyl.

19. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by R^5, where R^5 is heteroaryl.

20. A compound according to claim 19 in which R^4 represents 3-(imidazol-1-yl)-C_{1-3}alkyl).

21. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by R^5, where R^5 is C_{3-8}cycloalkyl.

22. A compound according to claim 21 in which R^4 represents straight or branched C_{1-3}alkyl substituted by C_{5-6}cycloalkyl.

23. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by R^5, where R^5 is C_{1-6}alkoxy.

24. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by R^5, where R^5 is halo.

25. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by R^5, where R^5 is an acidic functional group.

26. A compound according to claim 25 in which R^4 represents straight or branched C_{1-3}alkyl substituted by carboxy.

27. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by R^5, where R^5 is heterocycloalkyl.

28. A compound according to claim 27 in which R^4 represents straight or branched C_{1-3}alkyl substituted by 1,3-benzodioxol-5-yl or 1,4-benzodioxan-6-yl.

29. A compound according to any one of claims 1 to 15 in which R^4 represents straight or branched C_{1-6}alkyl substituted by $-NY^1Y^2$.

30. A compound according to claim 29 in which R^4 represents straight or branched C_{2-3}alkyl substituted by an N-linked 5-7 membered cyclic amine.

31. A compound according to claim 30 in which R^4 represents 3-(2-oxo-pyrrolidin-1-yl)-C_{2-3}alkyl.

32. A compound according to any one of claims 1 to 15 in which R^4 represents C_{1-4}alkenyl.

33. A compound according to any preceding claim in which Y represents carboxy.

34. A compound according to any one of claims 12 to 33 in which the group $-R^9-C(=O)-N(R^{11})-CH_2-C(=O)-NR^4-CH_2-CH_2-Y$ is attached at the ring 4 position.

35. A compound according to claim 12 in which R^4 represents C_{1-10}alkyl, C_{1-6}alkyl substituted by aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-6}alkoxy, halo or $-NY^1Y^2$, or R^4 represents C_{1-4}alkenyl; R^{11} represents hydrogen, C_{1-4}alkyl, C_{1-3}alkyl substituted by aryl, heteroaryl, C_{3-8}cycloalkyl or carboxy, or R^{11} represents C_{2-3}alkyl substituted by $-NY^1Y^2$; R^9 represents C_{1-4}alkylene; X^1 represents CR^2 where R^2 is C_{1-4}alkyl; X^2 represent CR^2 where R^2 is C_{1-4}alkoxy; Y represents carboxy; and the group $-R^9-C(=O)-N(R^{11})-CH_2-C(=O)-NR^4-CH_2-CH_2-Y$ is attached at the ring 4 position; and their prodrugs, and pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and their prodrugs.

36. A compound according to claim 1 selected from the following:
3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound A;
3-{(3,4-dimethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-amino}-propionic acid, Compound C;
3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-[3-(2-oxo-pyrrolidin-1-yl)-prop-1-yl]-amino}-propionic acid, Compound D;
3-[(2,3-dimethoxy-benzyl)-({2-[3-methoxy-4-(3-o-tolylureido)phenyl]-acetylamino}-acetyl)-amino]-propionic acid, Compound AO;
3-[N-(3,4-dimethoxybenzyl)-2-{2-[3-methoxy-4-(3-o-tolylureido)phenyl]acetylamino}acetamido]-propionic acid, Compound BD;
3-{[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-N-methylamino)-acetyl]-(3-carboxy-prop-1-yl)-amino}-propionic acid; Compound KW;
3-{(3-ethoxy-4-methoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LE;
3-{(3,4-diethoxy-benzyl)-[({[3-methoxy-4-(3-o-tolylureido)phenyl]-acetyl}-amino)-acetyl]-amino}-propionic acid; Compound LF;
and their prodrugs, and pharmaceutically acceptable salts and solvates of such compounds and their prodrugs.

37. 3-[N-(3,4-Dimethoxybenzyl)-2-{2-[3-methoxy-4-(3-o-tolylureido)phenyl]acetylamino}-acetamido]propionic acid, Compound BD, and its pharmaceutically acceptable salts and solvates.

38. A compound according to claim 1 in which n is 1, 2 or 3.

39. A pharmaceutical composition comprising an effective amount of a compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, in association with a pharmaceutically acceptable carrier or excipient.

40. A compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, for use in therapy.

41. A compound according to claim 1 or a corresponding or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

42. A composition according to claim 39 for use in the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

43. A compound or composition according to claim 1 or 39 respectively for use in the treatment of inflammatory diseases.

44. A compound or composition according to claim 1 or 39 respectively for use in the treatment of asthma.

45. Use of a compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, in the manufacture of a medicament for the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion.

46. Use of a compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof, in the manufacture of a medicament for the treatment of asthma.

47. A method for the treatment of a human or non-human animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of $\alpha 4\beta 1$ mediated cell adhesion comprising administering to said patient an effective amount of a compound according to claim 1 or a corresponding prodrug, or a pharmaceutically acceptable salt or solvate of such a compound or a prodrug thereof.

48. A compound as substantially hereinbefore described with references to the Examples.

49. A resin selected from Resin 1, Resin 2, Resin 3, Resin 4, Resin 5, Resin 6, Resin 7 and Resin 8.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/GB 98/03859

A. CLASSIFICATIO SUBJECT MATTER
IPC 6 C0 75/42 C07D207/27 A61K31/17 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 36859 A (G. D. SEARLE & CO) 9 October 1997 see claims	1
A	WO 97 36862 A (G. D. SEARLE & CO) 9 October 1997 see claims	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 1999	09/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Van Geyt, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 98/03859

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: 48,49
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
Claim 48 does not fulfil the requirements of Rule 6.2(a) PCT.
Claim 49 is unclear (Art. 6 PCT).

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claim 47 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

In view of the extremely broad Markush claims, the search was executed with due regard to the Guidelines, B-III, 2.1, 2.3 read in conjunction with 3.7 and Article 92 EPC, i.e. the search was executed with particular emphasis on the inventive concept, as illustrated by the explicitely claimed compounds and examples.
The search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 98/03859

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9736859 A	09-10-1997	AU 2536097 A	22-10-1997
		EP 0891325 A	20-01-1999
WO 9736862 A	09-10-1997	AU 2337097 A	22-10-1997
		EP 0889877 A	13-01-1999